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CONTENTS

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(Vol. XLIX of the continuous series)

PAGE

Tuberculous Polyserositis. By Roy M. Acheson. With Plates 12 to 14 159

Some Effects of Severe Chronic Anaemia on the Circulatory System. By William Whitaker 175

Renal Tubular Acidosis. By G. L. Foss, C. B. Perry, and F. J. Y. Wood. With Plates 15 and 16 185

Haematogenous Brain Abscess in Cyanotic Congenital Heart Disease. By E. J. Newton. With Plates 17 and 18 . . 201

A Five-year Assessment of Patients in a Controlled Trial of Streptomycin, Para-Aminosalicylic Acid, and Streptomycin plus Para-Aminosalicylic Acid, in Pulmonary Tuberculosis. By Wallace Fox and Ian Sutherland 221

The Neuropsychiatric Syndrome associated with Hepatic Cirrhosis and an Extensive Portal Collateral Circulation. By W. H. J. Summerskill, Esther A. Davidson, Sheila Sherlock, and R. E. Steiner. With Plates 19 and 20 . 245

Neuropathy in Peripheral Vascular Disease. By E. C. Hutchinson and L. A. Liversedge 267

An Investigation of Prolonged Insulin Resistance in a Case of Diabetes Mellitus. By J. R. Presland and the late C. M. Todd 275

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TUBERCULOUS POLYSEROSITIS[1]

By ROY M. ACHESON

(From the Tuberculous Meningitis Research Unit, Radcliffe Infirmary, Oxford)

With Plates 12 to 14

A SEROUS membrane may become involved by the disease processes of tuberculosis in one of two ways; it may react to the infection of the bacillus in the manner characteristic of the other tissues of the body and produce tubercles, or it may form a serous effusion. It is common to find one membrane (usually the pleura or peritoneum) involved in either of these ways. Very occasionally, however, pleural, pericardial, and peritoneal sacs are affected, and a complex tuberculous polyserositis develops. In its most acute, proliferative form this is a rapidly progressive condition. The patient dies within a few months of the onset, and at post-mortem examination the serous membranes are found to be studded with tubercles; effusions are scanty or absent. The exudative form of the disease presents a very different picture. In the early stages considerable effusions occur in the great serous cavities; later the effusions are absorbed, leaving the parietal and visceral layers of the serosae densely fibrotic and adherent to each other. In this way constrictive pericarditis often ensues. The present paper is concerned with the exudative type of tuberculous polyserositis. The clinical literature is reviewed, and a patient successfully treated in Oxford discussed. Then a survey is made of vital statistics and animal experiments that throw some light on the aetiology and pathogenesis of the disease. With these data in mind suggestions are made about treatment.

Definition of the Syndrome as a Clinical Entity

The first reports of the syndrome in recent times are attributed to the Paris school of the early nineteenth century. Feitu (1820) described peritonitis complicated by *phlegmasies* of the pericardium, the pleura, and the arachnoid. Broussais (1822) in his *Histoires des phlegmasies* more than once made mention of 'une inflammation chronique consécutive des séreuses'. Although neither of these authors specifically referred to tuberculosis as the cause of the effusions, it is probable that tuberculous infection was responsible, at least, for the pathological appearances described by Feitu. The earliest recorded case history is probably that of the Dutchman van Deen (1846, 1847), but apart from this and other isolated case reports no advance was made in the understanding of the syndrome until 1880. At that time, and for 30 years, the literature took on a curiously national flavour. Between 1880 and 1900 important complementary,

[1] Received July 8, 1955

but independent, contributions were made from Italy and Germany, and after the turn of the century a synthesis between these schools was achieved in America by Nicholls (1902), and to a much greater extent by Kelly (1903). The first of the Italians was Luigi Concato, who in 1880 read a paper to the Ninth Congress of the Italian Medical Association (published late in 1881) entitled *Sulla poliorromenite scrofolosa o tisi delle sierose*. He described two patients. One had a fulminating proliferative polyserositis, and died in three months. The other was ill for two years, during which he had effusions into all four great serous sacs, before dying of tuberculous meningitis. Concato, who, it must be remembered, was writing before the isolation of the tubercle bacillus by Koch, pointed out that *poliorromenite scrofolosa*, like phthisis, might follow an acute or chronic course, but that it was invariably fatal. Picchini (1891, 1892) described Concato's *poliorromenite* in great detail. He treated 50 patients in whom two or more membranes were involved. Five of these patients had effusions into all the great serous sacs (*poliorromenite più complessa*), and form the largest single series in the literature. He reported the clinical and pathological findings with meticulous care, and there can be no doubt of the honesty and accuracy of his observations. This monograph, which is unobtainable in the medical libraries of this country, deserves more attention than it has received. While the Italians were centring their attention on tuberculosis of the serosae, the German school was approaching the problem from a different angle. Curschmann (1884) described a case of ascites of six years' duration, in which he had failed to find the expected periportal cirrhosis *post mortem*. Instead, there was gross hyaline thickening of the liver capsule, a condition he called *Zuckergussleber*. There is little doubt that his patient, a woman of 50 years, had tuberculous polyserositis. It was, however, neither the multiple involvement of the serosae nor the tuberculous origin of the disease, but the gross 'sugar icing' of the liver, which appealed to Curschmann's imagination. Pick (1896) collected a series of three cases of the syndrome described by Curschmann. One was found to be tuberculous at necropsy, and in one tuberculous infection was suspected in life, but was not confirmed *post mortem*. Pick believed that the root of the trouble lay in the pericardium. This, he thought, was the site of some obscure inflammation which eventually caused its fibrosis, which in turn embarrassed the action of the heart. The resulting circulatory disturbance in the liver led to an increase of connective tissue in its capsule; this obstructed the portal circulation, and so ascites was formed. Because this was his theory of the pathogenesis of the syndrome, he called it *pericarditische Pseudolebercirrhose*. Although the pleurae were diseased in all his three cases, he made little reference to this circumstance in his explanation of the pathological process.

It was Kelly (1903) who pieced together these hitherto unrelated fragments to make the coherent clinical pattern which he called multiple serositis. Osler (1905) considered this paper to be the authoritative work on the subject. In the first place, Kelly suggested that the *poliorromenite scrofolosa* of Concato and the *pericarditische Pseudolebercirrhose* of Pick were essentially the same disease in different stages, the latter a consequence of the former. The disease began

with an insidious and generalized inflammation of the serous membranes, which reacted by becoming thickened and fibrotic, and in certain areas hyalinized. Secondly, he argued that the chronic ascites was not necessarily due either to peritonitis (White, 1892) or to perihepatitis (Curschmann, 1884; Pick, 1896). In the later stages of the disease, at least, he thought it much more likely to be caused by heart failure resulting from constrictive pericarditis. Apart from a shortened and inferior version of Picchini's original monograph, written in 1929, only case reports have appeared in the literature since Kelly's time. Thus his critical and scholarly discourse still holds pride of place in the literature of the syndrome. Both his hypotheses receive ample support from the following case.

Case History

(No. R.I. 88801/48). In December 1947 an 11-year-old girl was noticed to be pale and listless. A few weeks later she was seen in consultation, and was found to have pleural effusions, abdominal distension, engorgement of the jugular veins, and hepatomegaly. X-rays showed that the mediastinal lymph-nodes were grossly enlarged. A provisional diagnosis was made of Hodgkin's disease, and she was admitted to the Radcliffe Infirmary. Here she rapidly developed effusions into all four serous sacs, and, since the Mantoux test showed her to be acutely sensitive to old tuberculin,[2] the diagnosis was changed to one of tuberculous polyserositis. This was soon confirmed by isolation of *M. tuberculosis* from the pleural fluid. In spite of full supporting treatment and regular paracenteses from all four serous sacs, she grew steadily worse until, in January 1949, it seemed that she must die from heart failure within the next few weeks, and she was sent home. At this time she was noticed to have slight but persistent albuminuria.

During the following months she rallied; the pericardial and pleural effusions largely resolved, though the ascites persisted and required frequent tapping. In October 1949 she was admitted for reassessment. At this time she was a morose, underdeveloped child, looking at least three years less than her age. She resented any examination, and her conversation and manner were hostile. It was found that, though she was no longer in cardiac failure, she had suffered a recent miliary spread, as witnessed by choroidal retinal tubercles and by characteristic fine mottling in the chest X-ray. In addition to the ascites there was a small tuberculous focus in the apex of the right lung, and active tuberculosis in both kidneys and in the second lumbar vertebra. *M. tuberculosis* was isolated from the sputum, ascitic fluid, and urine, and the blood-urea was found to be 76 mg. per 100 ml. Photographs of the patient at this time are shown in Plate 12, Fig. 2. Since streptomycin had now become available, chemotherapy was begun immediately; but, as this was a case of widespread, progressive disease in a child who had already been ill for 18 months, it was decided to supplement the chemotherapy with intermittent intramuscular injections of tuberculin, a form of treatment that already yielded encouraging results in tuberculous meningitis.[3] In view of the increased blood-urea the streptomycin dosage was carefully controlled by repeated assay of the blood level. Weekly lumbar punctures were also performed, lest the patient should develop

[2] This test was carried out personally by Dr. R. L. Vollum, Director of Public Health Laboratories, Oxford, who states that never in his experience has he seen so intense a reaction to O.T. 1/100,000.

[3] For the theory and practice of this therapeutic régime see Smith (1953).

tuberculous meningitis. Even when these were timed to coincide with the systemic tuberculin reactions, no abnormality was ever found in the cerebrospinal fluid. In February 1950 she developed an intestinal obstruction, which was relieved by laparotomy.

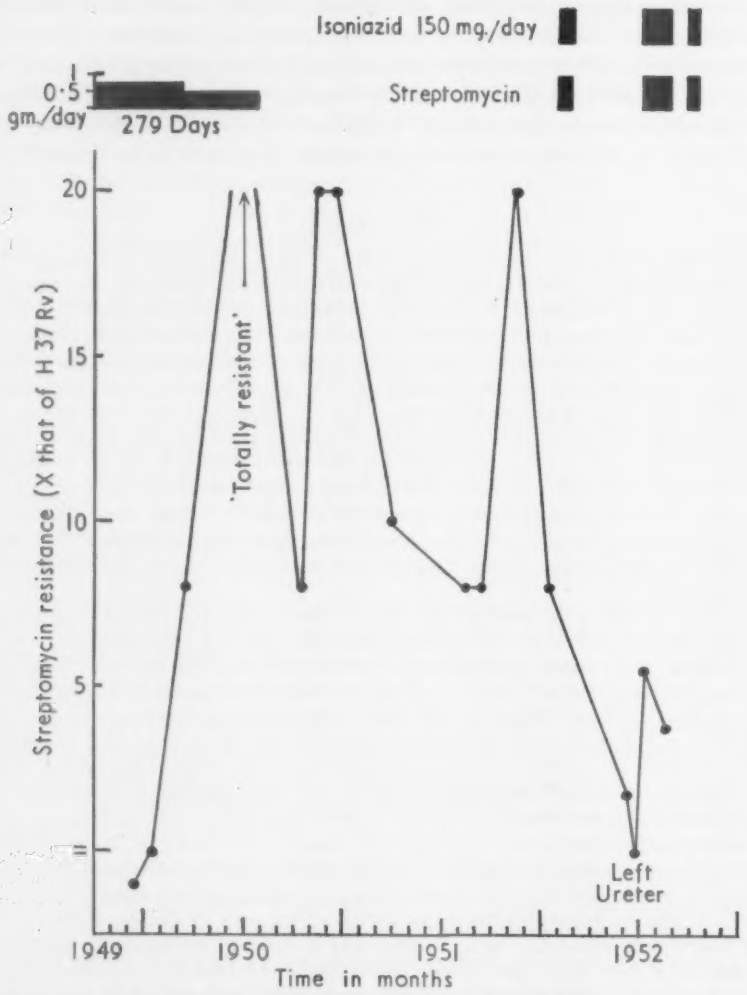

FIG. 1. Graphic representation of the streptomycin resistance of *M. tuberculosis* isolated from the patient's urine, compared with that of H 37 Rv. Details of chemotherapy are shown.

She received streptomycin and tuberculin for nine consecutive months. Details of the chemotherapy given then and later in her illness, together with data regarding the streptomycin sensitivity of the tubercle bacilli recovered from her urine, are shown graphically in Fig. 1. She improved steadily throughout this period, and by June 1950 she was up and about; the miliary lesions and

the pulmonary focus had healed, and the tiny focus in her spine appeared inactive. Although the urine contained considerable quantities of albumin, repeated cultures were sterile for *M. tuberculosis*, and the blood-urea had fallen to 22 mg. per 100 ml. In spite of this improvement she still had gross ascites and, moreover, once more had partial heart failure. Six weeks later she again began to excrete *M. tuberculosis* from the left kidney. At this stage she was given 12 months' leave from hospital to continue her convalescence at home.

She was readmitted in October 1951, and though her general condition was much improved she now showed the full syndrome of constrictive pericarditis, with oedema of the face and upper limbs, and persistent ascites. Pericardectomy was therefore performed in December 1951. The effect of this operation was remarkable: the oedema and ascites disappeared, her exercise tolerance improved, and menstruation began. At last she developed a zest for living; she no longer resented the hospital staff, and she expressed the ambition to become a nurse. In fact, both mentally and physically, she approached her true age of 15 years. Nevertheless she continued to excrete *M. tuberculosis* from the left kidney. As this organ was now apparently the only active tuberculous centre in her body, it was removed in September 1952. Since that time the urine has been sterile, but albuminuria has persisted. She remained convalescent until December 1952, when she suffered several attacks of severe biliary colic. Her gall-bladder was removed, and she has remained well from that time onwards. She is now a member of the hospital secretarial staff, and leads a full, healthy life (Plate 14, Fig. 7).

Pathological findings

Peritoneum removed at laparotomy (Plate 12, Fig. 3). Over the serous membrane, which was normal in thickness, lay a massive fibrinous exudate. The subserosal tissue was the site of an intense inflammatory reaction, the predominant cells in the section being eosinophile granulocytes. No acid-fast bacilli were identified in this section.

Gall-bladder with peritoneum. At operation several small stones were found in the cystic duct. Microscopically the epithelium was shown to be thickened and oedematous. The peritoneum covering the organ was thickened and fibrotic (Plate 13, Fig. 4).

Pericardium. The specimen had suffered considerably from trauma, but was found to be greatly thickened. Microscopically it consisted entirely of hyaline and fibrous tissue, in which foci of calcification were present.

Kidney (Plate 13, Figs. 5 and 6). Macroscopically one small cavity was found, surrounded by dense fibrous tissue, and communicating with the pelvis. Microscopic examination suggested that two distinct pathological processes were at work. In the first place, areas of typical tuberculous granulation tissue were spread diffusely throughout the organ. Many of these contained giant-cell systems, and appeared active. Secondly, there were irregular areas of glomerular damage, bearing no obvious relationship in their distribution to the tuberculosis just described. The lesions varied from a fibrosis and thickening of Bowman's capsule to a total destruction and hyalinization of the glomeruli. In areas where tuberculous infiltration impinged upon these damaged glomeruli, the glomeruli appeared to escape invasion or replacement by the tuberculous process. The tubules showed considerable post-mortem degeneration, but apart from this, and from a generalized dilatation, there was little pathological change. There was no oedema of the renal interstitium. Tests for amyloid disease in this tissue were negative.

Thus, as Kelly (1903) predicted, this patient changed from being a case of

Concato's disease, with the inflamed peritoneum seen in Plate 12, Fig. 3, to a case of Pick's disease, with the thickened membrane seen in Plate 13, Fig. 4. The fact that latterly her ascites was due to heart failure was borne out by her response to pericardectomy.

Aetiology and Pathogenesis

Although Picchini (1892, 1929) maintained that all cases of polyserositis were due to the tubercle bacillus, and supported his contention in a convincing manner, this view is not widely held. Kelly (1903) believed that Koch's bacillus might be causative in certain cases, but that in the majority an unspecified micro-organism of low virulence was to blame; other authors have been more specific, *S. typhi* (Weiss, 1876), *H. pertussis* (Riedel, 1892) and *Treponema pallidum* (Henoch, 1895), all having been incriminated; the condition has also been considered to be a manifestation of rheumatism, nephritis, and diffuse lupus erythematosus. It is beyond the scope of the present paper to discuss the merit of these various claims. Some evidence concerning the part played by *M. tuberculosis*, a very common organism in the pathogenesis of this most uncommon syndrome, is gleaned from vital statistics and animal experiments.

Vital statistics. When the reported cases of complex tuberculous polyserositis are analysed by age and sex (Table I), it becomes evident that it is predominantly a disease of adolescence. It is commoner in male than female subjects, especially in the adolescent period. In both these respects it bears a striking resemblance to primary tuberculous pleural effusion, as will be seen in Table II, which shows two recent unselected series analysed in a similar manner. Primary tuberculous pleural effusion, as its name implies, is usually thought to be a sign of a fresh tuberculous infection (Thompson, 1946; Waring, 1955). The similarity in age and sex incidence between these two syndromes suggests that complex tuberculous polyserositis may also be a manifestation of primary tuberculosis.

Animal experiments. All effective experiment in tuberculosis dates from the work of Robert Koch. In 1878 he formulated his postulates, and four years later he reported the isolation and culture of the tubercle bacillus. In 1891 he showed that, if *M. tuberculosis* was introduced into the skin of a guinea-pig, the tissue reaction of an animal already suffering from tuberculosis differed radically from that of a normal animal. He demonstrated that this difference was related to the fact that infected animals were sensitive to tuberculin, a protein found in the broth in which the bacillus had been cultured. From this it was a natural step to the concept of allergy to tuberculin, put forward by von Pirquet (1907), and to the demonstration of an intradermal diagnostic test by Mantoux (1908). Rist, Leon-Kindberg, and Rolland (1914), Paterson (1917), and Pinner (1928) showed that Koch's phenomenon had an analogy in the serous membranes of the peritoneal and pleural cavities. It was only in the previously infected, sensitized animal that an effusion occurred in immediate response to the injection of the bacillus. Howard and deVeer (1936) took this work a stage further by producing an experimental polyserositis. They showed that injection of tuberculin into the peritoneal cavity of a sensitized guinea-pig induced transient effusions in all

four great serous sacs. If these injections were repeated during several weeks the effusions formed again and again, and finally the membranes became fibrotic.

In discussing the experimental induction of effusion with bacilli, Paterson

TABLE I

Age and Sex of Patients in reported cases of Chronic Tuberculous Polyserositis

	Age group (years)							
Sex	*5–14*	*15–24*	*25–34*	*35–44*	*45–54*	*55–64*	*65–74*	*Total*
Male	Harris (1895) Nachod (1898) Cabot (1898) Allen (1936)	Corazza (1868) Weinberg (1887) Mott (2) (1887) Picchini (3) (1891) Broadbent (1895) Pick (2) (1896) Bozzolo (1897) Patella (1898) Nicholls (1902) Herrick (1903) Clarke (1929)	Baronchelli (1881) Signorini (1883)	Concato (1881) Wagner (1883–4) Lamb (1920–1) Bezançon, de Gennes, Bernard, and Oumansky (1932) Guyer and Smith (1936) Vierordt (1888)	Herrick (1903) Orr-Ewing (1921)		Whitcher (1924)	
Total	4	15	2	6	2	..	1	30
Female	Acheson (1956)	Fox (1877) Weinberg (1887) Picchini (1891)	Pennato (1889) Picchini (1891)	Taylor (1900)	Curschmann (1884) Vierordt (1888) Burrell, Hare, and Ross (1929)	Lamb (1920–1)		
Total	1	3	2	1	3	1	..	11
Sex not stated					Petrasu (1871)			1
Total	5	18	4	7	6	1	1	42

(1917) wrote: 'With the development of the effusion there is also a marked production of fibrin, which is deposited on the pleural surfaces, both visceral and parietal, giving them a shaggy appearance. The fibrin is not exuded evenly from the whole pleural surface, but forms small areas on which the bacilli lodge.' This fibrin has a twofold importance. In the first place, its fate is to be organized and to be replaced by fibrous tissue. The tissue distortion which results is the basis of a crippling sequel of tuberculosis of a serous membrane. Not only does it cause cicatrization of the pleura and reduction of vital capacity, but it leads to constrictive pericarditis, which is one of the lethal complications of polyserositis. Secondly, Petroff and Stewart (1925) showed that, when tubercle bacilli were injected into the peritoneal cavity of a sensitized rabbit, the bacilli could be recovered only with great difficulty from the resulting effusion 48 hours later, whereas in the unsensitized control animal they were detected relatively easily. This was presumably because the bacilli were enmeshed in fibrin in the

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Total	4	15	2	6	2	..	1	30
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sensitized animal, an occurrence which may account for the difficulty experienced by bacteriologists in isolating the bacillus from tuberculous serous effusions. Some bacilli, however, remain free in the fluid, as was shown by Aschoff, who claimed to have isolated *M. tuberculosis* from 80 per cent. of 'sterile' primary pleural effusions. Thus it has been shown that the serous effusion and the accompanying

TABLE II

Age and Sex Incidence of Primary Tuberculous Pleural Effusion in Two Recent Unselected Series

Place and author	*Sex*	*Age group (years)* 0–4	5–14	15–24	25–34	35–44	45–54	55–64	*Total*
Ealing (Thompson, 1946)	Male	1	13	67	17	7	2	1	108
	Female	1	12	46	13	2	4	2	80
Bedfordshire (Wynn-Williams and Shaw, 1955 *a*, *b*)	Male	3	21	40	16	6	3	..	89
	Female	1	11	31	17	6	4	..	70
Total	Male	4	34	107	33	13	5	1	197
	Female	2	23	77	30	8	8	2	150
	Sexes combined	6	57	184	63	21	13	3	347

pleocytosis[4] are a tuberculin reaction. Presumably, in the majority of clinical cases, the tuberculin is being released on to the sensitized membrane by the bacilli which are enmeshed in the fibrin. What is more, the fibrin itself may be the result of a strictly localized, but intense, tuberculin reaction.

Complicating Pathology and Associated Conditions

Several of the recorded cases share complicating pathological changes with each other and with the Oxford case. Some of these changes are worthy of comment.

The involvement of other membranes of similar structure. In the case of Bezançon, de Gennes, Bernard, and Oumansky (1932) tuberculous synovitis of several joints was reported. The quadriceps bursa (Burrell, Hare, and Ross, 1929) and the right elbow-joint (Harris, 1895) also developed infected tuberculous effusions. Baronchelli (1881) described a tuberculous hydrocele in his patient. In view of the close anatomical relationship between the peritoneum and the tunica vaginalis of the testis, it is surprising that this complication has not been reported more often.

The involvement of the kidney. The pathological changes in the kidney in the Oxford case are particularly interesting. The patient was known to be passing albumin in her urine during the early phase of her illness, when all four serous sacs were freely exuding serous fluid. At that time the albuminuria was thought to be due to heart failure. In the light of the subsequent pathological findings it is possible that it was due to inflammation of Bowman's capsule. The association between nephritic changes and polyserositis has been recorded more than once, but the renal lesion has never been ascribed to the same process as the

[4] The cytology of this pleocytosis has been described by Dworski, Smith, and Gardner (1925), Randerath (1927), Swithinbank, Smith, and Vollum (1953), and Bosanquet, Daniel, and Vollum (1953).

serositis. Kelly (1903) referred to nephritis as a possible cause of serositis. In one of the cases described by Carr (1923) hyaline casts and albumin were found in the urine, and *post mortem* the kidneys showed a moderate chronic diffuse nephritis. Lamb's patient (1920–1) also had albuminuria, and many hyaline casts were seen; since the patient was still living when the paper was written, no histological findings are available. Herrick (1903) described Bowman's capsule as being 'slightly thickened' in one of his cases. Picchini (1892) described a case which resembles that of our patient very closely in this respect. He wrote of a man aged 56 years, who died with tuberculous serositis of both pleurae and of the pericardium. Apart from the tuberculous infiltration, which was scanty, histological sections of the kidney showed areas where the glomeruli were diseased, and other areas where the parenchyma was normal. The diseased glomeruli had thickened capsules, and the space inside was reduced; comparatively speaking, the vascular tufts were less implicated in the disease process. In places entire glomeruli were degenerate. The tubules tended to be deprived of their epithelium. The similarity between this description and that recorded on page 163 is striking. The pathogenesis of these changes is obscure, but it may not be inappropriate to point out that Rist and Leon-Kindberg (1913) produced acute glomerular nephritis in the tuberculin-sensitive dog by intracardiac injection of tubercle bacilli, and that similar changes have been produced in tuberculin-sensitive swine by large doses of intra-arterial tuberculin (Long and Finner, 1928; McGregor, 1928). Renal damage is by no means an invariable finding, and in the cases of Concato (1881), Mott (1887), Harris (1895), and Burrell, Hare, and Ross (1929), to mention a few instances, normal kidneys were found *post mortem*. Concato (1881), Harris (1895), Taylor (1900), Bezançon, de Gennes, Bernard, and Oumansky (1932), and Allen (1936) recorded the absence of albuminuria in their patients.

Tuberculous polyserositis and gall-bladder disease. Nicholls (1902) and Kelly (1903) referred to the association between gall-bladder disease and polyserositis, suggesting that the former caused the latter. In the Oxford case the gall-bladder and cystic duct were covered with fibrotic peritoneum. It seems probable that this fibrosis caused the formation of stones by impeding the flow of bile.

Polyserositis and gonorrhoea. The patient of Bezançon, de Gennes, Bernard, and Oumansky (1932) suffered gonococcal arthritis before he developed tuberculous synovitis. In addition, the patients of Concato (1881), Lamb (1920–1), Carr (1923), and Clarke (1929) gave a history of gonorrhoea. Kelly's patient (1903) also gave a history of gonorrhoea, but the polyserositis was never proved to be tuberculous. Although this association of diseases is worthy of comment, no further conclusions can be drawn from it on the present evidence.

Duration of Illness and Cause of Death

The recorded cases are analysed as to duration of illness and cause of death in Table III. It will be seen that 10 of the 42 patients (24 per cent.) developed progressive blood-borne disease, and that, on average, this was the cause of the earliest deaths. Thirteen (31 per cent.) died of heart failure, and of these the

patient with the shortest illness (Taylor's (1900) case) also had a pulmonary tuberculous lesion. The other causes of death were acute peritonitis (Fox, 1877), multiple emboli (Vierordt, 1888), and pneumonia (Lamb, 1920–1). The average duration of illness in the eight patients listed in column E was eight and a half years. Of the survivors, only Lamb's patient had lived more than eight and a half years from the onset of his illness.

Treatment

The analysis in the previous paragraph shows that the problem in treatment is twofold: (1) the prevention of thickening and fibrosis of the serous membrane; (2) the control of haematogenous spread of tuberculous infection. It is in fact similar in essence, if not in emphasis, to the problem of treating primary tuberculous pleural effusion. Recent trends in the management of this syndrome have been reviewed elsewhere (Acheson, 1955). Chemotherapy *per se* has been found to be useless in the prevention of pleural thickening, and in the case under discussion gross fibrosis of the peritoneum and pericardium developed in spite of streptomycin. Of the methods suggested for the suppression of this reaction, the combination of adrenal corticosteroids and chemotherapy is probably the most suitable in tuberculous polyserositis. Ebert and Barclay's (1952) report that cortisone greatly modifies the tuberculin reaction in the ear chamber of the rabbit, together with the finding of Long and Miles (1950) that it reduces tuberculin sensitivity, form a good experimental basis for the treatment. Several authors (Karlson and Gainer, 1952; Bulkeley, 1953; Houghton, 1954; Johnson and Davey, 1954; Ashby and Grant, 1955) have reported that the combination of adrenal corticosteroid therapy with adequate antibiotics is safe in tuberculosis. Sors and Trocmé (1954) have used corticotrophin, given in a slow intravenous infusion, together with streptomycin and isoniazid, in the treatment of a few cases of tuberculous pleural effusion. They claim to have achieved startling resolution of fluid in patients whose effusions were of recent origin. Thus intravenous corticotrophin, or possibly oral cortisone, given with chemotherapy, might well be justified in an attempt to prevent fibrosis of the serous membranes, and therefore constriction of the pericardium. Should these measures fail, pericardectomy should be undertaken without hesitation when the patient's general condition permits.

The control of parenchymatous tuberculosis must depend upon sustained chemotherapy. Recent reports from France (Brouet, Marche, and Chrétien, 1954; Bernard, Kreis, Chrétien, and Jullien, 1955) suggest that isoniazid with streptomycin given every third day continues to be effective over very long periods of time. The Medical Research Council (1955) have stated that daily streptomycin and isoniazid, given for three months, is one of the best combinations they have tried. Smith (1955) has given these two drugs daily in combination for very much longer periods, without any serious increase in drug resistance. For these reasons, and because it is a most unpleasant and unsavoury medicament, several authorities (Brouet, Marche, and Chrétien, 1954; Mackay-Dick

and Rothnie, 1954; Smith, 1955) have abandoned the use of *p*-aminosalicyclic acid, and depend upon the combination of streptomycin and isoniazid. Isoniazid permeates living membranes freely (Elmendorf, Cawthon, Muschenheim, and McDermott, 1952; Gehrt, 1952; Mackaness, 1952), and streptomycin has been shown to pass through the inflamed pleura in bactericidal quantities (Zintel,

TABLE III

Duration and Outcome of Illness in Recorded Cases of Complex Exudative Tuberculous Polyserositis

	Duration of illness (months)						
Cause of death	A *Less than 6*	B *7–12*	C *13–24*	D *25–48*	E *Over 48*	F *Unknown*	*Number of patients*
Heart failure		Taylor (1900)	Pick (2) (1896)	Mott (2) (1887) Harris (1895)	Curschmann (1884) Cabot (1898) Patella (1898) Burrell, Hare, and Ross (1929) Guyer and Smith (1936)	Picchini (2) (1891)	13
Miliary tuberculosis or tuberculous meningitis	Weinberg (1887) Broadbent (1895) Whitcher (1924)	Nachod (1898)	Concato (1881)	Wagner (1883–4) Vierordt (1888) Herrick (1903)		Pennato (1889) Nicholls (1902)	10
Other			Fox (1877)		Vierordt* (1884)	Lamb (1920–1)	3
Unknown		Weinberg (1887)		Bezançon, de Gennes, Bernard, and Oumansky (1932)		Corazza (1868) Petrasu (1871) Signorini (1883) Picchini (2) (1891)	7
Patients survived	Baronchelli (1881)		Orr-Ewing (1921) Clarke (1929) Allen (1936)	Bozzolo (1897) Herrick (1903)	Lamb (1920–1) Acheson (1956)	Picchini (1891)	9
Total	4	3	7	9	8	11	42

* Vierordt's patient died of pulmonary and cerebral emboli, but showed clinical and post-mortem evidence of chronic heart failure.

Flippin, Nichols, Wiley, and Rhoads, 1945; Steenken, d'Esopo, and Wolinsky, 1947). It was found in the ascitic fluid of our Oxford patient in concentrations of between 7 and 10 μg. per 100 ml. on many occasions. Tuberculin was used in the present case as an experimental measure, because it had been found to be most effective in certain other types of tuberculosis (Smith and Vollum, 1950; Smith, 1953). It is possible that it played a part in the healing of the many parenchymal lesions, and it may also have helped to keep the bacillus sufficiently sensitive to streptomycin. The evidence gleaned from this and other cases suggests that it does not penetrate the serous membranes, and it is unlikely that it had any direct influence on the serositis itself.

Discussion

Although the clinical and pathological features of the disease are widely agreed, there have been few suggestions as to why the serous membranes are picked out in such a peculiar and characteristic manner. Complex tuberculous polyserositis, unlike tuberculous meningitis, is not associated with the common haematogenous miliary spread. Nicholls (1902) wrote: 'So far as we know no instance has been met with in which there was a generalized haematogenic development of the lesions'; and in the many clinical reports to which Nicholls had no access the present author has found nothing to refute this remark. Thirteen of the recorded cases (Curschmann, 1884; Mott, 1887 (two); Picchini, 1891 (two); Harris, 1895; Pick, 1896 (two); Cabot, 1898; Patella, 1898; Taylor, 1900; Burrell, Hare, and Ross, 1929; Guyer and Smith, 1936) showed no evidence of disseminated miliary lesions *post mortem*; and, in the majority of the patients who died of miliary tuberculosis or tuberculous meningitis, the case reports suggest that the haematogenous dissemination of the infection was a separate episode, occurring after the polyserositis had developed. This was certainly true of our Oxford patient, whose serous effusions had already begun to be absorbed when she suffered her miliary spread. Moreover, Rich (1951) stated that he knew of no laboratory worker who had succeeded in inducing a serous effusion in an animal, whether tuberculin-sensitive or not, by introducing the bacillus into the blood-stream. Thus we must assume that this uncommon disease is due to some idiosyncrasy in the organism or in the individual. Cantu (1894) thought that the disease might be due to an atypical bacillus, perhaps the avian bacillus. He brought no evidence, nor has any subsequent author, to support this view. The disease is much more likely to be due to an unusual reaction by the host. Evidence has already been reviewed above which suggests that it is a rare primary manifestation of tuberculosis, and therefore associated with recent Mantoux conversion. Several authors (Herrick, 1903; Burrell, Hare, and Ross, 1929; Bezançon, de Gennes, Bernard, and Oumansky, 1932; Allen, 1936) have stated that their patients were tuberculin-sensitive. Only Bezançon and his collaborators referred to the degree of sensitivity, which in their patient, as in the Oxford patient, was extreme. Although no general conclusion can be deduced from two cases, the implication is that complex tuberculous polyserositis differs from primary pleural effusion in this respect. It was found in the Prophit Survey (Daniels, Ridehalgh, and Springett, 1948) that acute tuberculin-sensitivity on conversion was more highly correlated with parenchymal tuberculosis than with pleural effusion. A much smaller study by North (1941) reported results which are in line with the Prophit findings. The theory has been put forward by some authorities (Picchini, 1891; Taylor, 1900; Burrell, Hare, and Ross, 1929) that complex tuberculous polyserositis is associated with a high degree of immunity to the tubercle bacillus. Apart from the fact that immunity to tuberculosis is a quality which defies measurement, their contention is not compatible with the fact that 24 per cent. of the untreated patients die of progressive tuberculosis within four years of the onset of their symptoms.

Although some indication of the pathogenesis can be derived from the general characteristics of age, sex, sensitivity, and immunity, the final solution to the riddle must be in careful consideration of the individual case. In the first place, it seems highly probable that the serous sacs which contain effusions are also directly infected by the tubercle bacillus. This is in keeping with current opinion as to the pathogenesis of serous effusion (Thompson, 1949; Waring, 1955), and, although Howard and deVeer (1936) succeeded in inducing transient effusions in animals with tuberculin, these effusions resolved within a very few days. To the author's knowledge no experimental worker has succeeded in inducing a long-lasting effusion with tuberculin. In the Oxford case the bacillus was recovered from the pleural and peritoneal fluids, and it was probably only because of the technical difficulties referred to above that it was not isolated from all the sacs.

Not many of the recorded clinical histories are sufficiently detailed to ascertain which serous sac becomes infected first. Picchini (1891, 1929) asserted that, although pleural or pericardial effusions might be the first to come to the physician's notice, the disease usually started in the peritoneum. Experimentally, it was only by inoculating tuberculin into the peritoneal cavity of the sensitized animal that Howard and deVeer (1936) could produce effusions in all the other serous sacs. Thus the peritoneal cavity is probably the most usual seat of origin. The bacillus could arrive there by one of two routes: (1) direct spread from an infected organ lined by the serous membrane of the cavity; (2) spread through the lymphatics. Rich (1951) believed that a tuberculous pleural effusion is probably due to the discharge of small quantities of infected caseous material from the lung into the pleural cavity. If this theory is true, presumably effusions could be induced in the other serous sacs by similar means. However, tuberculosis of the organs underlying the serosae has not always been demonstrated in polyserositis. Several of the recorded cases—for instance, one of Mott (1887), and one of Weinberg (1887)—showed tuberculosis of the lymphatics or the serous membranes *post mortem*, but none of any of the underlying organs. In the absence of tuberculous disease of the viscera, it is difficult to see how caseous material could gain direct access to the peritoneal cavity. The suggestion that the lymphatic system is the vehicle of spread has had the support of Picchini (1891, 1929), Taylor (1900), Kelly (1903), Lamb (1920–1), and Whitcher (1924). There is no doubt that many of the patients reported have had tuberculous involvement of the mesenteric and mediastinal lymph-nodes, and lymphadenitis was such a predominant feature in our patient that Hodgkin's disease was at first thought to be the diagnosis. If the serous disease starts as an infection of the peritoneal cavity, and if bacilli are removed thence by lymphatic channels, they will pass up through the mediastinum in close relationship to the other three serous sacs. A further argument in favour of lymphatic spread is the suggestion, already made, that complex tuberculous polyserositis is a manifestation of primary tuberculosis. Lymphatic involvement is one of the dominant features of all primary tuberculous infection.

Even though this is the case, and though infected lymphatic nodes have been

accepted as an origin of primary serous pleural effusion (Thompson, 1949), it is difficult to see how the organism passes out of the lymphatic channels into the serous sacs. This would have to occur either by retrograde spread along the channels draining the sac, or through the walls of an infected node. The author does not know of either of these methods of spread having been demonstrated experimentally. On the evidence, however, the lymphatic theory seems least objectionable. Although the other two theories, or a combination of the three, may hold in individual cases, it seems likely that the syndrome is a manifestation of primary tuberculous infection, and that the lymphatic system plays a major part in its pathogenesis.

Acknowledgements

The laparotomy, nephrectomy, and cholecystectomy were performed by Mr. Arthur Elliot Smith, and the pericardectomy by Mr. G. C. Laurie Pile. I am grateful to them, and to Dr. A. M. Cooke, Dr. Frank Ridehalgh, Dr. Victoria Smallpeice, and Dr. Honor Smith, who were in turn responsible for the treatment of the patient, for permission to publish this report. Surgeon Lieutenant-Commander John Wylie, R.N., Dr. Peter Daniel, and Dr. R. H. Cowdell kindly gave their opinions on the pathological specimens. I wish to thank several of these senior colleagues, and in particular Dr. Honor Smith, for criticizing this paper.

Dr. Wynn-Williams and Dr. Shaw, of the Bedford and Luton Chest Clinics, went to considerable trouble to let me have the analysis shown in Table II. The photomicrographs are the work of Mr. B. H. Glass. I obtained microfilms of several of the papers quoted through the courtesy of the Armed Forces Medical Library, Washington, U.S.A.

Summary and Conclusions

The early stage of complex tuberculous polyserositis, when there are multiple effusions, is due to an active tuberculous process; the ascites and heart failure in the later stages of the disease are due to fibrosis and hyalinization of the serous membranes following the initial inflammation.

In the 42 cases discussed (41 from previous reports) the syndrome has an age and sex incidence very similar to that of primary tuberculous serous effusion, and is commonest between the 15th and 24th years.

A very rare syndrome itself, it may occasionally be complicated by gall-bladder disease or nephritic changes. Of untreated patients, 24 per cent. die of miliary tuberculosis within four years of the onset of the syndrome; the majority of the remainder die of heart failure due to constrictive pericarditis, after an illness which lasts, on average, eight or nine years. Twenty-two per cent. of the patients reported in the literature were living when their records were published, but only one had survived for more than nine years.

It is suggested that the disease should be treated with daily streptomycin and isoniazid for many months. Evidence is reviewed which indicates that concomitant adrenal corticosteroid therapy may prevent fibrosis of the serous membranes. Pericardectomy should be undertaken if the last measure fails.

Although the pathogenesis of the syndrome remains obscure, it is concluded that this is an unusual manifestation of primary tuberculous infection, and that extensive lymphatic involvement may be instrumental in producing the multiple serous effusions.

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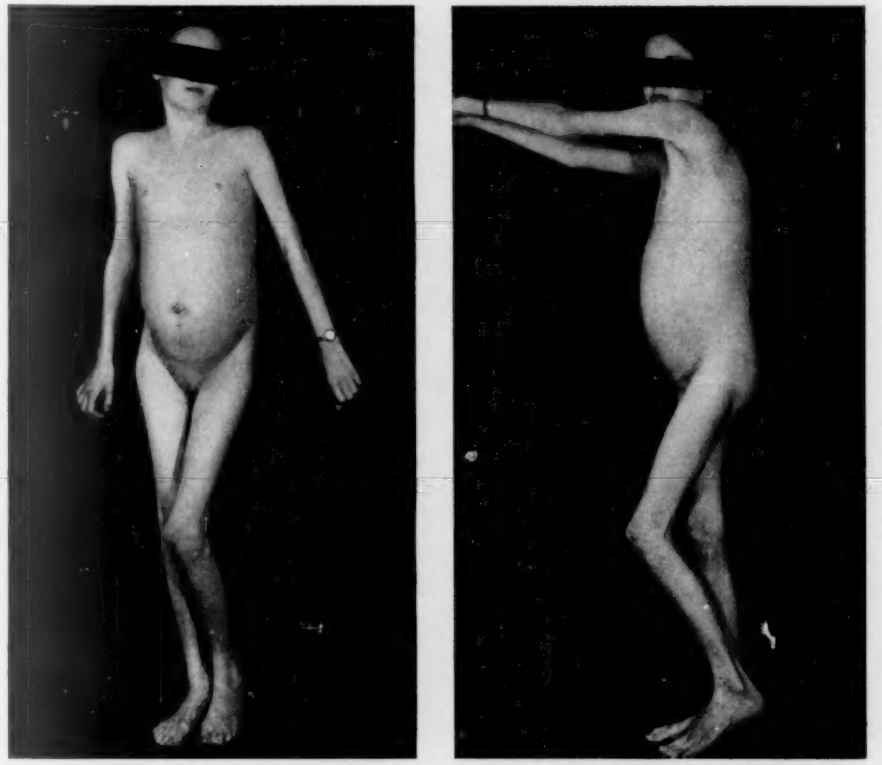

FIG. 2. The patient in October 1949, at the time when miliary spread of her tuberculosis was diagnosed. Note the general cachexia, contrasting with a distended, ascitic abdomen

FIG. 3. Section of peritoneum taken at laparotomy in February 1950. The dark-staining cells are eosinophile granulocytes. P = peritoneum; F = fibrinous exudate; S = subserosal tissue

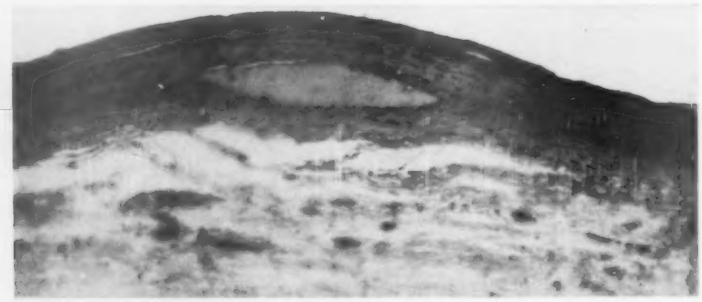

FIG. 4. Section of the peritoneum covering the gall-bladder, removed in December 1952. Note the thickening and fibrosis

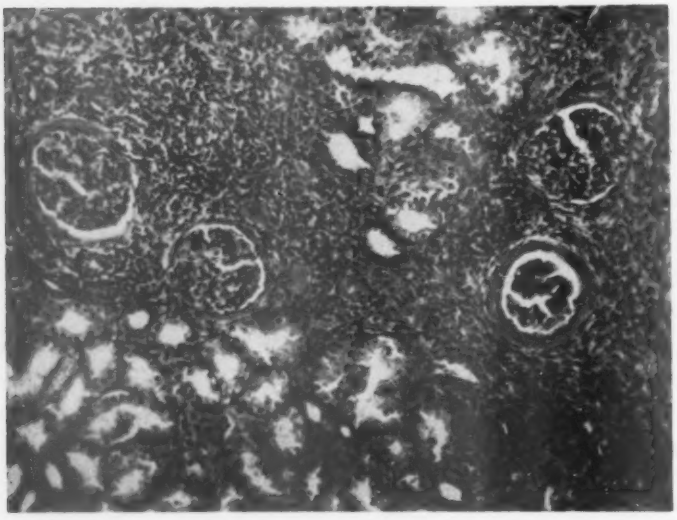

FIG. 5. Section of the kidney, showing the thickening of Bowman's capsule. This field is on the edge of a tubercle, which is responsible for the round-cell infiltration. The tubules are dilated, and show some post-mortem degeneration

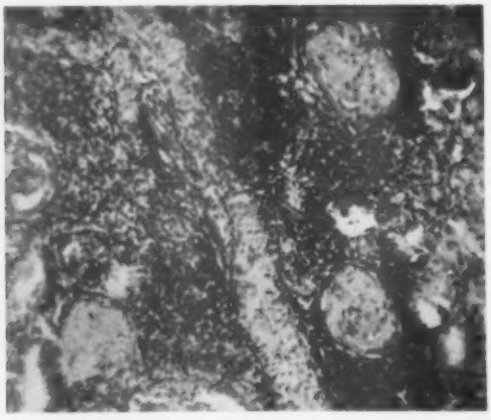

FIG. 6. Another section of renal tissue, showing glomeruli which have undergone general hyalinization

FIG. 7. The patient in January 1955. Her waist measurement is now 27 inches

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SOME EFFECTS OF SEVERE CHRONIC ANAEMIA ON THE CIRCULATORY SYSTEM[1]

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Plesch's (1909) demonstration of a high cardiac output in anaemic patients was confirmed by many observers, including Fahr and Ronzone (1922), Dautrebande (1925), Liljestrand and Stenström (1925–6), Richards and Strauss (1928), Grollman (1932); Starr, Collins, and Wood (1933) and Nielsen (1934), who also used indirect methods of estimating the gases in mixed venous blood; and Sharpey-Schafer (1944) and Brannon, Merrill, Warren, and Stead (1945), who employed cardiac catheterization to obtain samples of mixed venous blood for gas analysis. The proposition that anaemic patients had a high cardiac output was attractive, since clinical examination of these patients usually revealed signs of an increased peripheral blood-flow, termed the hyperkinetic syndrome by Harrison (1939). Recent studies of blood-flow to specific organs have shown, however, that an increase in cardiac output is not the only important alteration in the circulation caused by anaemia. By plethysmographic studies Abramson, Fierst, and Flachs (1943) found that the muscle blood-flow in the arms was increased, while the skin blood-flow was decreased. Heyman, Patterson, and Duke (1952) showed that the cerebral blood-flow was increased. Bradley and Bradley (1947) found an abnormally low renal blood-flow, and suggested that there was a mechanism in anaemic patients, similar to that observed in patients suffering from acute loss of blood or shock, which diverted blood from the kidneys to organs where it was more urgently needed, such as the heart and brain. These observations indicated that there was an abnormal distribution of blood in anaemic patients, which was possibly an adjustment as important as the change in cardiac output. The purpose of the present study was to investigate the circulatory system of patients with severe chronic anaemia by comparing observations made before and after treatment, and to assess the significance of abnormal features. Particular attention was given to abnormalities of the renal circulation, and these abnormalities have been considered in relation to heart failure complicating anaemia and to hypertension appearing after treatment.

Patients Studied and Methods

Ten patients, nine of whom were female, were studied (see Table). Eight (Cases 1, 2, 3, 4, 7, 8, 9, and 10) suffered from macrocytic anaemia of the Addisonian type, one (Case 5) from carcinomatosis due to breast cancer, and one

[1] Received October 3, 1955.

(Case 6) from chronic gastrointestinal bleeding. One female patient with Addison's anaemia (Case 3) also had thyrotoxicosis, which had been partially but inadequately treated by thiouracil. Three others (Cases 1, 4, and 10) and the patient with carcinomatosis (Case 5) had congestive heart failure, judged from the presence of peripheral oedema and elevation of the jugular venous pressure above the sternal angle in all phases of respiration. The man who had Addison's anaemia (Case 9) had in addition syphilitic aortic incompetence. One of the female patients with Addison's anaemia complicated by congestive heart failure (Case 4) also had chronic nephritis. When first studied, all the patients appeared to be adjusted to a severe degree of chronic anaemia, and with one exception were untreated. One patient (Case 4), with Addison's anaemia and chronic nephritis, received vitamin B_{12} and a transfusion of one pint of packed red blood-cells 10 days before investigation, but was still in congestive heart failure when first studied. The observations were repeated after a period of three to four weeks, during which all the patients received specific anti-anaemic therapy and blood transfusions, none receiving a transfusion within a week of the second study. All four patients with congestive heart failure recovered from this complication before they were reinvestigated, and did not require any maintenance therapy to prevent its recurrence.

All observations were made about two hours after a meal, with the subjects lying comfortably in bed. Cardiac output was calculated by the Fick principle from the oxygen consumption, measured by collecting expired air in a Douglas bag, and from the difference in oxygen-content of arterial blood and mixed venous blood, the latter being withdrawn from the right auricle through a cardiac catheter previously introduced under fluoroscopic control. The haemoglobin-content of each blood sample was measured by a photoelectric colorimeter, and from this the oxygen capacity was determined; the percentage oxygen-saturation was measured by a direct spectrophotometric method; and from these results the oxygen-content of the sample was estimated. Renal blood-flow was calculated from the effective renal plasma-flow and the haematocrit reading. Effective renal plasma-flow was measured by sodium-*p*-aminohippurate clearance, and the glomerular filtration rate by inulin clearance, the technique being that described by Dick and Davies (1949). Urine was collected for two accurately timed periods of about 20 minutes, and the clearance values used were the average of those obtained for each collection period. The filtration fraction, that fraction of the plasma passing through the kidney which is filtered by the glomeruli, was calculated by dividing the glomerular filtration rate by the effective renal plasma-flow. The validity of *p*-aminohippuric-acid clearance as a measurement of effective renal plasma-flow in patients with anaemia was established by Warren, Brannon, and Merrill (1944), who showed that the extraction of this substance was not reduced in anaemic patients. Samples of renal venous blood were taken from one patient (Case 7) in the present series at the time of both studies, and the renal extraction of *p*-aminohippuric acid was 86 per cent. before and 87 per cent. after treatment of the anaemia, which are normal values for this technique. The arterial systolic and diastolic blood-

pressures were recorded sphygmomanometrically, and the value of the arterial mean blood-pressure was assumed to be equal to the diastolic blood-pressure plus one-third of the pulse pressure. The total vascular resistance, in dynes per second per cm.$^{-5}$, was calculated by dividing the product of the arterial mean blood-pressure in centimetres of mercury, the density of mercury, and the acceleration due to gravity, by the cardiac output in millilitres per second. The renal vascular resistance was similarly estimated, the perfusion-pressure being taken as the arterial mean blood-pressure minus the renal venous pressure, which was assumed to be equal to the right auricular blood-pressure measured by cardiac catheterization. The renal fraction of the cardiac output was used to express renal blood-flow as a percentage of total cardiac output.

Results

The results of the present investigation, uncorrected for body surface-area, are shown in the Table, and are referred to throughout the discussion which follows.

Discussion

Many of the findings in the general circulation in the present series are in accord with those of the previous observers who have been cited above.

Cardiac output. Of nine cases in which the cardiac output was recorded, the initial values were abnormally high in seven (Cases 1, 2, 3, 5, 7, 8, and 9). The changes found after treatment were similar to those observed by Nielsen (1934): the cardiac output fell in seven patients in whom it had been abnormally high, and also in one (Case 4) whose resting cardiac output when she was anaemic was less than 4·6 litres per minute per sq. m. body-surface, which Donald, Bishop, Cumming, and Wade (1953) considered the upper limit of normal. One patient (Case 6), who showed no fall in cardiac output with treatment, had the highest initial haemoglobin level, 8·4 gm. per 100 ml., which is higher than the critical level of 7 gm. per 100 ml. below which Brannon, Merrill, Warren, and Stead (1945) found that the cardiac output in the resting state was usually raised. From a review of all available data Blumgart and Altschule (1949) found that there was no striking deviation from normal in the oxygen consumption of the body as a consequence of anaemia, and in the present series there was no consistent change in oxygen uptake with treatment. The samples of mixed venous blood were less saturated with oxygen before than after treatment, showing that a greater fraction of available oxygen was being utilized in the anaemic state. Sharpey-Schafer (1944) thought that 80 to 90 per cent. of the available oxygen was removed from the blood in some cases of severe anaemia; but such a degree of extraction did not occur in the present series, in which the lowest oxygen-saturation in mixed venous blood was 39 per cent. The majority of samples of mixed venous blood were 55 to 65 per cent. saturated with oxygen before treatment, which indicates a degree of oxygen extraction similar to that found by Bishop, Donald, and Wade (1955) in a series of patients with severe anaemia. In spite of the removal of a greater fraction of oxygen in all the

Circulatory Studies on Patients with Chronic Anaemia Before and After Treatment

Case number	*Age (years)*	*Sex*	*Body-surface area (sq. m.)*	*Diagnosis*		*Heart-rate/min.*	*Arterial blood-pressure (mm. Hg)*	*Arterial mean blood-pressure (mm. Hg)*	*Oxygen consumption (ml./min.)*	*Mixed venous oxygen-saturation (%)*	*Arterial oxygen-saturation (%)*	*Arteriovenous oxygen difference (ml./100 ml.)*	*Cardiac output (l./min.)*	*Mean blood-pressure in right auricle (mm. Hg)*	*Effective renal plasma-flow (ml./min.)*	*Glomerular filtration rate (ml./min.)*	*Filtration fraction*	*Renal blood-flow (ml./min.)*	*Haematocrit (%)*	*Haemoglobin (gm./100 ml.)*	*Renal fraction of cardiac output (%)*	*Total vascular resistance (dynes/sec./cm.$^{-5}$)*	*Renal vascular resistance (dynes/sec./cm.$^{-5}$)*
1	69	F	1·5	Addison's anaemia	A	92	145/45	78	136	48	91	1·8	7·7	+8*	250	78	0·31	285	12	3·2	3·7	808	19,400
					B	70	185/75	102	146	80	94	2·8	5·2	−5	318	74	0·23	530	40	12·5	10·2	1,540	15,350
2	60	F	1·4	Addison's anaemia	A	104	130/50	77	198	39	98	2·3	8·6	+1	409	86	0·21	445	8	2·7	5·2	715	13,050
					B	100	185/80	115	140	80	97	2·8	5·0	−5	525	123	0·23	840	38	12·0	16·8	1,840	10,800
3	59	F	1·25	Addison's anaemia and partially treated thyrotoxicosis	A	170	150/20	63	185	64	96	2·3	8·0	+4	263	72	0·27	316	17	5·0	3·9	630	14,000
					B	104	130/55	77	187	71	94	3·6	5·2	0	375	83	0·22	625	40	12·2	12·0	1,175	9,425
4	61	F	1·27	Addison's anaemia and chronic nephritis	A	80	150/75	100	162	61	95	3·2	5·1	+2*	115	31	0·26	153	25	6·7	3·0	1,560	49,300
					B	65	205/100	135	158	67	96	5·3	3·1	−6	130	39	0·30	232	44	12·9	7·5	3,508	45,500
5	39	F	1·38	Carcinomatosis	A	116	110/55	83	102	63	99	1·1	9·3	+6*	171	46	0·27	188	9	2·3	2·0	710	31,400
					B	90	120/80	93	165	73	96	3·8	4·4	−4	228	50	0·22	356	36	11·7	8·0	1,665	20,600
6	45	F	1·66	Chronic gastro-intestinal bleeding	A	84	145/85	105	240	64	94	3·5	7·0	0	449	75	0·16	625	28	8·4	8·9	1,190	12,850
					B	84	130/80	97	240	81	99	3·1	8·0	−5	549	131	0·24	970	43	13·6	12·1	957	12,000
7	65	F	1·4	Addison's anaemia	A	100	135/70	92	215	64	95	2·8	7·7	−3	479	97	0·19	580	17	6·0	7·5	955	12,380
					B	80	145/75	98	184	74	95	3·7	4·9	−2	387	99	0·25	645	40	12·1	13·3	1,600	12,000
8	64	F	1·61	Addison's anaemia	A	100	170/80	110	232	62	95	2·3	10·0	0	303	68	0·22	365	17	6·0	3·7	880	23,200
					B	84	190/100	130	265	72	97	4·7	5·6	−1	402	76	0·19	660	39	11·0	11·8	1,855	15,300
9	51	M	1·42	Addison's anaemia and syphilitic aortic incompetence	A	100	145/50	82	225	55	98	2·2	10·2	−1	362	88	0·25	407	11	4·0	4·0	640	15,780
					B	96	160/45	93	270	80	97	2·9	9·3	−1	425	70	0·16	655	35	11·3	7·0	795	10,950
10	68	F	1·32	Addison's anaemia	A	88	140/60	87	..	..	..	..	..	J.V.P. +7*	248	58	0·23	288	14	4·5	..	..	21,600
					B	84	190/90	124	..	..	..	..	..	J.V.P. 0	460	88	0·19	820	44	13·8	..	..	11,700

A = Before treatment.
B = After treatment.

* = Accompanied by congestive heart failure.
J.V.P. = jugular venous pressure.

anaemic patients, the total amount of oxygen obtained from each unit of volume of blood, shown by the arteriovenous oxygen difference, was, with the exception of Case 6, less before than after treatment, because of the small oxygen capacity of anaemic blood. These observations support the view that the high cardiac output associated with anaemia cannot be ascribed to an abnormally high oxygen consumption, but that, together with increased removal of available oxygen from blood passing through the capillaries, it provides a means by which a normal supply of oxygen is maintained to the body when the oxygen capacity of blood is reduced.

Heart-rate. In all the patients in this series, except one (Case 6) in whom the cardiac output fell, the resting pulse-rate was higher before treatment of the anaemia. The majority, however, showed only a small change in heart-rate compared with the change in cardiac output, and it was obvious that a high heart-rate was not primarily responsible for the high cardiac output. Stewart, Crane, and Deitrick (1937) noted that increased stroke-volume was a feature of the 'high output' state in anaemic patients. Bishop, Donald, and Wade (1955), who found that the pulse-rate was surprisingly low in many of their severely anaemic patients, also thought that an increase in stroke-volume, and not in heart-rate, was the important factor maintaining a high cardiac output at rest. Although figures for stroke-volume were not calculated in the present series, it is apparent that the change in cardiac output with treatment cannot be explained entirely by change in heart-rate, and that the stroke-volume must have been higher in the anaemic state. The only atypical findings were in Case 3; this patient, with a partially treated thyrotoxicosis, had a smaller stroke-volume before treatment.

Venous pressure. In the present series a fall in venous pressure occurred with treatment in all instances except Cases 7 and 9, and was most striking in those patients (Cases 1, 4, 5, and 10) who recovered from congestive heart failure. Sharpey-Schafer (1944) thought that a high venous pressure played a major part in maintaining the high cardiac output in anaemic patients. This is contrary to the view of Stewart, Crane, and Deitrick (1937), Brannon, Merrill, Warren, and Stead (1945), and Bishop, Donald, and Wade (1955), who believed that the high cardiac output occurred independently of elevation of venous pressure. The present findings support this latter view, since there was little change in the right auricular blood-pressure in Cases 7 and 8, in which the cardiac output fell remarkably with treatment. Bishop, Donald, and Wade (1955) believed that a raised venous pressure in an anaemic patient was a sign of reduced cardiac reserve, rather than a critical factor producing a high cardiac output.

Blood-pressure and total peripheral vascular resistance. The blood-pressure recordings before treatment were characteristic of the state of high cardiac output in anaemia, and showed high pulse-pressures and low diastolic pressures. The changes observed with treatment were similar to those described by Stewart, Crane, and Deitrick (1937); all the patients except two (Cases 6 and 9) developed higher diastolic blood-pressures, and all except two (Cases 3 and 6) higher systolic

blood-pressures. Three patients (Cases 4, 8, and 10) had abnormally high blood-pressures after treatment, and when they were subsequently observed as out-patients even higher pressures were recorded. Similar very striking increases in blood-pressure were observed by Stewart, Crane, and Deitrick (1937) and, since hypertension follows experimentally-induced renal ischaemia, it is impossible to disregard the severe renal ischaemia and anoxia which occur in anaemia as possible causes of subsequent arterial hypertension. Bradley and Bradley (1947) provided no support for this hypothesis, since they found that hypertension did not usually develop in the course of chronic anaemia. From the present results, however, and from those of Stewart, Crane, and Deitrick (1937), it appears that severe anaemia must either mask hypertension or predispose to this complication. The mean blood-pressures, calculated from the systolic and diastolic blood-pressures, were less before than after treatment, except in Case 6. Since lower perfusion-pressures were sustaining higher levels of cardiac output, it was obvious that the total resistance to blood-flow was reduced in the anaemic patients. When the total vascular resistance was calculated, an increased value was found after treatment in all patients whose cardiac output was initially high. Although a state of high output develops only with haemoglobin levels below 7 gm. per 100 ml., it is not believed that anoxia caused by anaemia of this severity acts directly on the peripheral blood-vessels to lower the vascular resistance. Hatcher, Sunahara, Edholm, and Woolner (1954) found that, when severe anaemia had been caused in dogs by bleeding, the cardiac output rose slowly for about one week, and that after rapid correction of severe anaemia the cardiac output fell slowly. These authors accepted Sharpey-Schafer's (1952) suggestion that the development of a state of high output was related to a slow-acting or slowly elaborated humoral mechanism.

Renal circulation. A reduction in renal blood-flow was thought by Bradley and Bradley (1947) to be a most striking feature of chronic anaemia, and this belief is supported by the present results. These results show abnormally low initial levels of renal blood-flow, which increased with treatment in all the patients. The increases ranged from about 10 per cent. in Case 7 to about 200 per cent. in Case 10. Davies and Kilpatrick (1951), using a similar technique, estimated the normal range of renal blood-flow at between 981 and 1,483 ml. per minute. In the present series the persistence of low values after treatment can be largely accounted for by a natural decline in renal blood-flow in the elderly, and by the small stature of the patients. The extremely low rates of blood-flow and low clearance values in Case 4 were due to associated chronic nephritis. Since the cardiac output fell in all the patients except one (Case 6), while the renal blood-flow increased, there must have been a marked increase in the fraction of the cardiac output passing to the kidneys. Estimation of the renal fraction of the cardiac output showed that it was abnormally small in the anaemic patients, and that it increased towards normal, which is 15 to 20 per cent., with treatment. Renal vasoconstriction, generalized vasodilatation elsewhere, or a combination of both these mechanisms, are possible causes of an abnormally small fraction of the cardiac output flowing to the kidneys.

Although an abnormally low total vascular resistance and an abnormally low perfusion-pressure have been noted previously as characteristic of severe anaemia, these abnormalities did not entirely account for the abnormal renal blood-flow in the present series. In the majority of cases the change in renal blood-flow was greater than could be explained by change in head of pressure, and calculation of the renal resistances indicated an initial renal vasoconstriction which diminished with recovery. Bradley and Bradley (1947), who first showed that there was renal vasoconstriction in patients with severe anaemia, thought that it occurred in both afferent and efferent arterioles, but predominantly in the afferent, since the filtration fractions were low. In the present series there was no consistent relation between the fall in renal vascular resistance with treatment and the change in the filtration fraction, a fact which suggests that renal vasoconstriction in anaemia does not affect the afferent or efferent arteriole predominantly. In calculating vascular resistances no allowance was made for alterations in the haematocrit level, since within the range of the present series blood viscosity would not be greatly altered; but the changes in renal resistance certainly cannot be accounted for by an alteration in blood viscosity, since the resistance was greatest when the least viscous anaemic blood flowed to the kidney.

The effective renal plasma-flow increased with treatment in all cases except Case 7, but only in Case 6 returned to the normal range, which Davies and Kilpatrick (1951), using a similar technique, found to be between 540 ml. and 817 ml. per minute. The reduction in renal plasma-flow with anaemia was not so great as the change in renal blood-flow, since the proportion of plasma in blood increased, as shown by the haematocrit level. Platt (1952) thought that there was possibly a mechanism which kept renal plasma-flow approximately normal in anaemia, and pointed out that it was obviously to the advantage of glomerular filtration for the blood to contain more than its normal quota of plasma when renal blood-flow was reduced. In the majority of cases the glomerular filtration rate was affected similarly to the renal plasma-flow. There were no gross abnormalities in the filtration fractions, and treatment did not cause any consistent change.

Congestive heart failure. The occurrence of congestive heart failure in the course of chronic anaemia has long been recognized, and has usually been attributed to the effects of anoxia on the myocardium, which have been evident from electrocardiographic changes and from post-mortem examination of the heart in fatal cases. It is equally reasonable, however, to assume that the development of peripheral oedema and elevation of the jugular venous pressure are primarily due to impairment of renal function. Strauss and Fox (1940) found that, when anaemic patients were loaded with salt and water, the magnitude of water retention varied inversely with the haemoglobin level, and they concluded that anaemia *per se* was a factor conducive to water retention. Bradley and Bradley (1947) also thought the impairment of salt and water excretion in patients with anaemia was primarily due to abnormal renal function, and that this was independent of elevation of jugular venous pressure.

There is undoubtedly severe renal anoxia in patients with gross anaemia, for the kidneys receive an abnormally small flow of blood containing an abnormally small amount of oxygen. If normal oxygen consumption is maintained, metabolism must occur at abnormally low oxygen tensions. Alternatively, if the kidneys can utilize oxygen only at high tensions, such as normally occur in renal venous blood, an abnormally small amount of oxygen is available. Either event will produce tissue anoxia, which might profoundly affect renal function and cause retention of salt and water. In the present series all four patients with congestive heart failure recovered completely from this complication with treatment of the anaemia. Only one of these patients (Case 10) showed a significant increase in the glomerular filtration rate; this circumstance suggests that abnormal tubular reabsorption, rather than an abnormal tubular load, was responsible for the impairment of salt and water excretion in the anaemic state.

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Summary

1. Features of the general and renal circulation were investigated, in 10 patients with severe chronic anaemia, before and after treatment.

2. The cardiac output fell with treatment in all cases, except one patient whose initial haemoglobin level was greater than 7 gm. per 100 ml. The high cardiac output in the anaemic patients was not related to an abnormally high oxygen consumption, but, together with increased removal of available oxygen, provided a normal amount of oxygen for the body.

3. Increased stroke-volume, rather than tachycardia, appeared to maintain the high cardiac output.

4. There was no direct relation between fall in cardiac output and fall in right auricular pressure with treatment. A high cardiac output appears to be independent of elevation of the venous pressure in patients with anaemia.

5. The anaemic patients had high pulse-pressures and low diastolic blood-pressures. After treatment three patients had abnormally high arterial blood-pressures, and it was concluded that severe anaemia either masked or predisposed to hypertension.

6. An overall vasodilatation was found to be associated with renal vasoconstriction in the anaemic patients. This selective alteration in peripheral vascular resistance produced an unusual distribution of blood, an abnormally small fraction of the cardiac output flowing to the kidneys.

7. The renal fraction of the cardiac output was reduced in the anaemic patients enough to cause the absolute renal blood-flow to be abnormally low, even though the cardiac output was raised. Renal anoxia seemed to be an inevitable sequel to a low renal blood-flow in anaemia, and has been discussed as a possible cause of salt and water retention, and of arterial hypertension after treatment.

8. The change in the haematocrit value prevented the striking alterations in renal blood-flow from markedly affecting the renal plasma-flow. The glomerular filtration rate was affected similarly to renal plasma-flow by anaemia. It was impossible to relate the disappearance of congestive heart failure, which occurred in four patients with treatment of the anaemia, to any change in tubular load.

9. There was no constant alteration in the filtration fraction with treatment, a fact which showed that renal vasoconstriction did not predominantly affect the afferent or efferent arteriole.

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RENAL TUBULAR ACIDOSIS[1]

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With Plates 15 and 16

During the past 20 years a rare clinical syndrome has been recorded, of which the essential feature seems to be a failure of the kidneys to produce a urine of normal acidity. The urine is alkaline or at the most weakly acid in reaction, of fixed specific gravity, and commonly of copious amount. Acid metabolites are excreted in combination with fixed base, and there results a constant loss from the body's stores of sodium, potassium, and calcium in varying proportions. At the same time, although the urine is alkaline, there is a systemic acidosis of unusual character in that a decrease in plasma-bicarbonate and an increase in plasma-chloride are associated with a low plasma inorganic phosphate. Of the several names given to this syndrome we have chosen the term renal tubular acidosis, and in the present paper describe five new cases. Synonymous terms are nephrocalcinosis infantum with hyperchloraemic acidosis (Boutourline-Young, 1949), nephrocalcinosis with rickets and dwarfism (Albright, Consolazio, Coombs, Sulkowitch, and Talbott, 1940), concomitance of chronic acidosis with late rickets (Boyd and Stearns, 1942), idiopathic renal acidosis (Stapleton, 1949), and renal acidosis resulting from tubular-insufficiency-without-glomerular-insufficiency (Albright, Burnett, Parson, Reifenstein, and Roos, 1946).

Renal tubular acidosis has been described in two groups of patients. The larger group consists of infants who have shown dehydration not due to diarrhoea, vomiting, or inadequate intake of fluids or salts, and in whom the disorder has often been fatal. Some apparent recoveries after treatment with citrate mixtures have been recorded. Examples of the syndrome in infants have been reported by Lightwood (1935), Lightwood, Maclagan, and Williams (1936), Butler, Wilson, and Farber (1936), Anderson (1939), Hartmann (1939), Peterman (1945), MacGregor (1948), and Boutourline-Young (1949). The second group of patients consists of older children and adults, who differ from the infants in the clinical history of their disorder. The duration of the illness is prolonged, and treatment with citrates and other alkalinizing salts produces clinical improvement, but not cure. Evidence will be presented to suggest that the renal defect is present from birth. Clinical manifestations of the disorder, however, while they may be found in early infancy, are often delayed until adolescence or adult life. Their pattern depends, for the most part, on the

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constant loss of basic ions that results from the inability of the kidneys to produce an acid urine. Loss of calcium may lead to rickety changes with easily-produced fractures, deformities, and stunted growth. Owing, presumably, to the greater insolubility of its salts in alkaline solutions, calcium tends to be deposited in the kidneys, with the formation of stones or of nephrocalcinosis. The passage *per urethram*, singly or repeatedly, of small calculi is a common complaint. Renal colic, constant pain in the loins, haematuria, or attacks of acute pyelonephritis are also found. Loss of potassium may lead to attacks of muscular weakness, varying from mild, transient episodes to more severe weakness lasting days at a time, and even to extensive, and sometimes fatal, paralysis of the limbs and trunk. The weakness tends to be present when the patient first wakes in the morning, but may develop at any time of day. In some patients disturbances of calcium metabolism dominate the clinical picture; in others muscular weakness is the more conspicuous feature, while most suffer from both abnormalities in varying degree at the same or different times. Polyuria and thirst are common complaints. The patients may feel tired and apathetic, probably because of potassium deficiency (Fourman, 1954). The water balance of patients with renal tubular acidosis seems precariously poised; an attack of vomiting for whatever reason, or even so simple a procedure as the restriction of fluid intake in the course of a urinary concentration test, may lead to serious dehydration. The patients often appear thin and frail.

Whether these two groups of patients—the infants on the one hand, the older children and adults on the other—are suffering from variations of the same disorder, or from syndromes biochemically similar but aetiologically distinct, is not at present known. The patients described in the present paper belong to the older group.

Case Reports

Case 1. A girl aged 7 years came under observation in March 1941. She had been a full-term baby, but at birth weighed only 5 lb., a fact which may not be of much significance, as her mother is small in stature, and the patient's two normal brothers weighed 6 lb. each at birth. The patient was artificially fed. She walked at 13 months of age, and was not backward in talking. Her growth, however, was very slow, but except for measles and whooping-cough she otherwise remained seemingly well until early in 1941. She then developed attacks of muscular weakness in the legs. These attacks began and ended suddenly; they lasted up to six hours, and when they were over the child appeared perfectly well. The arms were not seen to be affected. At no time had the child suffered from fits. Owing to the air-raids on Bristol in March 1941, the patient could not be admitted to hospital for investigation. Radiological examination of the skeleton, however, showed 'generalized subcalcification and ragged metaphyseal lipping, especially at the lower end of the femur and ulna, indicating rachitic changes'. There were also reported 'considerable nitrogen retention', some albuminuria, and fairly numerous leucocytes in the urinary deposit. The biochemical reports were destroyed by enemy action, and the exact figures are not known. On the basis of these findings a diagnosis of renal rickets was made, and sodium citrate and sodium bicarbonate, 1·32 gm. of each three times a day, were prescribed. In October 1941 it became possible to admit the patient to the Bristol Royal Hospital for Sick Children. Since taking the

citrate-bicarbonate mixture she had had no further attacks of weakness. She was very small for her age, her weight being only 26 lb. and her height 38 inches. A 'rickety rosary' was present, but there was no bossing of the skull, and no bowing of the legs. The deciduous teeth were carious; no permanent teeth had erupted. The heart, lungs, abdomen, and nervous system were clinically normal. A catheter specimen of urine showed a trace of albumin, but no leucocytes or casts; further specimens revealed no albumin. Culture of the urine was sterile. The blood non-protein nitrogen was 48 mg. per 100 ml., the serum-calcium 10·8 mg. per 100 ml., and the plasma inorganic phosphorus 3·8 mg. per 100 ml. A urine concentration test yielded a urine of maximum specific gravity 1,014; during the course of it, according to the hospital notes, the child became dehydrated. This statement, surprising at first sight, is no doubt correct in view of the happenings when the patient was in hospital in 1950. A urine dilution test in 1941 yielded a urine of minimum specific gravity of 1,008, and a urea concentration test a maximum of 1·4 gm. of urea per 100 ml. of urine. Radiological examination of the bones showed almost complete healing of the rachitic process.

The child was discharged from hospital in November 1941, the diagnosis appearing to be renal rickets. She continued to take her citrate-bicarbonate mixture, and periodically attended the out-patients' department for the next nine years. She remained well, and no alarming symptoms occurred until May 1950 when, at the age of 16 years, she complained one morning of a pain in her left thigh and of weakness in her arms and legs. She looked ill. She was unable to dress herself. She could not walk without assistance, and had to be carried downstairs. Her arms were so weak that she could not lift a jug to pour out a drink of water. By next day she had recovered, but thereafter she had further attacks of weakness which prevented her from going to work as a mill-hand. On one occasion, after going to work, she became too weak to cycle home, and had to be helped on to an omnibus. Generally, however, the weakness was first noticed in the morning, and wore off after a few hours. Apart from these attacks she felt well. In June 1950 the patient was admitted to the Bristol Royal Infirmary under the care of one of us (C. B. P.). In addition to her complaints of muscular weakness, she said that from time to time she passed large quantities of urine and always drank a lot of fluid, although, strangely, she denied being thirsty. She was thin, and only five feet in height, but normally proportioned; she was in fact as tall as her mother. Mentally she was normal. There was no clinical evidence of rickets. The secondary sexual characters were normal, and puberty had occurred at the age of 13 years. No abnormalities were found in the chest, heart, or abdomen. The blood-pressure was 120/70. The nervous system was clinically normal, the power of the limbs being good and the tendon-reflexes normal. During the first few days of her stay in hospital the patient had no symptoms, but on July 2 she complained of weakness of her arms. She had little power in them, and her grip was feeble; the right arm was more affected than the left. The arms were flaccid, but the tendon-reflexes were still obtainable. It was suspected that these attacks might be due to deficiency of potassium, a view that was supported by the electrocardiogram (Fig. 1). The serum-potassium was then found to be 2·3 mEq. per litre, serum-sodium 152 mEq. per litre, plasma-chloride 129 mEq. per litre, plasma-bicarbonate (as CO_2-combining power) 12 mEq. per litre, serum-calcium 5·3 mEq., and plasma inorganic phosphate (as phosphorus) 1·5 mEq. per litre. A plain X-ray photograph of the abdomen showed bilateral nephrocalcinosis, but no nephrolithiasis (Plate 15, Fig. 2.) The urine was alkaline. The bones appeared normal radiologically. Naked-eye and radiological examination of the teeth showed them to be well formed, with an intact lamina dura.

During the next few weeks the patient was kept under observation. The sodium-citrate-bicarbonate mixture was omitted, with startling and unexpected results. She remained well until July 30, when she began to menstruate, and in the evening vomited. Next morning she appeared ill, and was still vomiting. She complained that her legs and arms felt weak; her grip was poor, and she was

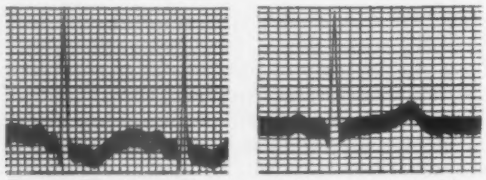

Fig. 1. Electrocardiogram of Case 1, (*a*) showing the effects of deficiency of potassium, (*b*) after recovery.

unable to lift her legs against gravity. She was given potassium citrate, 2 gm. by mouth, at 2.0 p.m. and again at 6.0 p.m. The following day she was much worse. She was dehydrated and drowsy. She was unable to move her legs and arms, and could not raise her head from the pillow. She complained of difficulty in breathing. The tendon-reflexes were absent. An electrocardiogram showed marked changes characteristic of potassium deficiency. The serum-potassium was only 1·7 mEq. per litre. During the day she received about 24 gm. of potassium chloride intravenously, the amount given being determined by frequent electrocardiography and serum-potassium estimations. By next morning the patient was better, although some weakness of the legs and arms was still present. At 9 a.m. the serum-potassium was 2·6 mEq. per litre, the plasma-chloride 129 mEq., and the plasma-bicarbonate 11 mEq. per litre. The patient was now given potassium citrate 2 gm. and sodium citrate 2 gm. four times a day by mouth. She rapidly recovered from now onward, and a week later the serum-sodium was 142 mEq. per litre, the serum-potassium 4·9 mEq., the plasma-chloride 108 mEq., the plasma-bicarbonate 24 mEq., and the serumin organic phosphate (as phosphorus) 2·0 mEq., per litre.

The patient was soon after discharged from hospital, and was given a mixture containing 2 gm. each of potassium citrate and sodium bicarbonate three times a day. She remained well, and her blood electrolytes returned to entirely normal levels. She was later readmitted for investigations, which included the following: (1) a urine dilution test: after two pints of water a prompt diuresis occurred, the specific gravity falling to 1,002; (2) a pitressin test: 0·07 unit of pitressin, given after she had taken two pints of water, produced a good inhibition of the diuresis; (3) a urea concentration test produced a maximum urea concentration of 0·84 gm. per 100 ml. of urine; (4) a urine concentration test gave a urine of maximum specific gravity 1,007; (5) after 50 gm. of glucose by mouth, the blood-sugar one hour later was 150 mg. per 100 ml. No glycosuria occurred.

The patient was admitted for the third time in October 1952. She had remained well, and was taking the citrate-bicarbonate mixture daily. A radiograph of the renal areas showed, however, that the nephrocalcinosis was slowly extending. In particular, some of the calcareous areas had become confluent. A urea concentration test gave a maximum urinary concentration of 1·4 gm. per 100 ml. The plasma non-protein nitrogen, serum-sodium, serum-potassium, plasma-chloride, plasma-bicarbonate, serum-calcium, and serum-phosphate were all normal. The serum alkaline phosphatase was 7 King-Armstrong units. The urine,

obtained by catheter, contained a trace of protein, no sugar, no red cells, no casts, and a very few white blood-cells. On her discharge she was given 1·5 gm. of potassium citrate and 2 gm. of sodium citrate three times a day. She has since remained well and gained weight. The blood electrolytes have remained normal, although radiography has again shown extension of the renal calcification (Plate 15, Fig. 2). In 1954 the patient was married, and in February of this year gave birth to a daughter weighing 7 lb. 2 oz. The pregnancy and confinement were normal, the citrate mixture being taken throughout. During the puerperium the patient developed a *Bact. coli* pyelitis, which fortunately was cured by streptomycin.

The patient's mother and brother were examined, and found to be normal.

Case 2. A married woman of 29 years had apparently been in good health until, in February 1948, she passed *per urethram* a stone of the size of a grape-pip. In September 1948 she had a sharp pain in the right loin, radiating to the groin. There was a high temperature, which caused her to go to bed for a fortnight. During the next 18 months there occurred two similar attacks of pain and fever. In 1950 she developed an aching pain in her left loin, which was almost constantly present until her admission to hospital a year later. During 1950 she felt progressively weaker, and was able to do less and less work in her home. On three occasions, while out of doors, she had sudden 'attacks', which she described as a sudden feeling of breathlessness with weakness of her body. On each occasion she had great difficulty in reaching her home. For the previous three years she had noticed increasing thirst, but she denied that she had polyuria. From time to time she had noticed cloudiness of her urine. In January 1951 the patient was admitted to the Bristol Royal Infirmary under the care of Mr. J. A. Pocock, who later referred her to one of us (C. B. P.).

On physical examination she was found to be of normal height and development, but was very thin, her weight being 7 st. 3 lb. There was some tenderness in the loins, but except for a blood-pressure of 85/60 no other physical abnormalities were found. A plain radiograph of the abdomen showed the presence of staghorn calculi in both kidneys, together with nephrocalcinosis. On January 10, 1951, blood analysis showed that the plasma non-protein nitrogen was 34 mg. per 100 ml., the serum-sodium 144 mEq. per litre, the serum-potassium 3·6 mEq., the plasma-chloride 114 mEq., the plasma-bicarbonate 22·5 mEq., the serum-protein 19 mEq., the serum-calcium 4·6 mEq., and the serum inorganic phosphate (as phosphorus) 1·7 mEq. per litre. The urine was slightly alkaline, the specific gravity 1,011, and there was a small amount of albumin, numerous pus-cells, and, on culture, a moderate growth of *Proteus vulgaris*. A urine concentration test yielded specimens of specific gravity 1,009, 1,008, 1,010, and 1,010. The urea clearance was 46 per cent. of normal, the blood-urea being 34 mg. per 100 ml. The creatinine clearance averaged 61 ml. per minute. The patient was treated with 3 gm. of potassium citrate three times a day, which changed the electrolytes to the following values: serum-sodium 143 mEq., serum-potassium 3·4 mEq., plasma-chloride 102 mEq., plasma-bicarbonate 34 mEq., and serum inorganic phosphate (as phosphorus) 2·8 mEq. per litre. Since the potassium level was still rather low, the patient was given, in addition to the potassium citrate, 2 gm. of potassium chloride three times a day. A fortnight later the serum-potassium was 4·8 mEq. per litre, plasma-chloride 101 mEq., and plasma-bicarbonate 29·5 mEq. per litre. The patient's urinary infection was more difficult to treat. Dihydrostreptomycin rendered the urine sterile, but the patient suffered vestibular damage, from which she only slowly recovered. The urinary infection later recurred, and was only temporarily controlled by chloramphenicol and aureomycin. She was discharged from hospital in May 1951, and attended

the out-patient clinic from time to time. So long as she took the potassium citrate and potassium chloride she felt better, although she periodically suffered from renal colic. The plasma electrolytes remained normal.

In July 1954 she was readmitted to hospital with an exacerbation of her urinary infection. She was inadvertently given 'sulphatriad', with serious effects. Within six days she was severely dehydrated, and appeared to be dying. She was treated energetically with large amounts of saline and, although three days later the blood non-protein nitrogen was 163 mg. per 100 ml., she rapidly recovered. In December 1954 she was treated at home with a sulphonamide compound, and was readmitted to hospital with severe vomiting and dehydration. She again responded favourably to treatment.

Case 3. This patient was born in 1928, her birth weight being 9½ lb. She was fed on cow's milk, and cut her first tooth at six months. The first dentition was complete at two and a half years. She walked at 16 months, but her legs soon became bent, particularly at the knees. She was treated in splints, and later underwent an operation for gross genu valgum. At the age of eight years an osteotomy was performed on the right femur. At the age of three years she had a slight attack of muscular weakness, and another at 16 years. These attacks became more frequent and, during the 12 months before she was seen by one of us (G. L. F.) in May 1946, they occurred every month. The patient was then 17¾ years of age. The onset of the attacks was usually at night, when she woke and called to her mother. During them she was only able to sit up with difficulty. The muscular weakness lasted from a few hours to two days.

In 1946 the parents became worried about their daughter because of her diminutive size, and because she had never menstruated. On direct questioning the patient said she was always thirsty. On examination she displayed gross disproportionate dwarfism and infantilism. Her apparent age was about 11 or 12 years, and the legs and arms were deformed, the trunk being normal. The head and face were normally developed, but the teeth were large, loose, and irregularly shaped, with alveolar absorption and pyorrhoea. The teeth were hard, and there was no sign of caries. There was very slight development of the breasts, with slight fullness behind the areolae. There was no hair in the axillae, and very scanty hair over the labia. The humerus was very short, disproportionately so when compared with the radius and ulna, and the upper end of the shaft was thickened. The femora were very short, and were bowed both anteroposteriorly and laterally. The tibiae were straight. The patient walked briskly with a peculiar waddle. Her weight was 4 st. 2 lb., and her height 46⅜ inches. No abnormalities were found in the heart, abdomen, or respiratory or nervous systems. In 1946 she was admitted to the Bristol Royal Infirmary under the care of Dr. Richard Clarke. The urine had a specific gravity of 1,002, and contained a trace of protein and some pus-cells, but on culture was sterile. The maximum specific gravity of the urine during a concentration test was 1,005. The plasma-bicarbonate was 17·6 mEq. per litre, the plasma-chloride 116 mEq., the serum-calcium 5·2 mEq., and the serum inorganic phosphate (as phosphorus) 1·6 mEq. per litre. The blood non-protein nitrogen was 63 mg. per 100 ml., and the serum alkaline phosphatase 55 King-Armstrong units per 100 ml. The blood Wassermann and Kahn tests were negative. Radiological examination of the skeleton showed a general infantilism, with a bone age of approximately 10 to 12 years. There was a general lack of calcification, with softening and deformities, chiefly in the lower extremities. There was evidence of late rickets. In the renal areas there were numerous calcifications, and two large calculi in the left ureter. Intravenous pyelography showed a left

hydronephrosis due to a stone in the ureter. Pseudo-fractures were seen in the femur. The diagnosis of nephrocalcinosis with rickets and dwarfism was made.

Treatment and progress. From July 1946 the patient was given a diet rich in calcium and phosphorus, and 50,000 units of calciferol daily, together with a mixture containing citric acid 140 gm. and sodium citrate 98 gm. made up with chloroform water to a litre, of which 20 ml. were taken thrice daily. After a month she lost her craving for water. In September she was given methyltestosterone 5 mg. and dienoestrol 0·3 mg. daily. In October radiological examination of the wrist showed that the rickets was healing. In November the blood non-protein nitrogen was 78 mg. per 100 ml. On December 4 treatment with calciferol and dienoestrol was stopped, and from January 3 to 8, 1947, she had her first menstrual period. Dienoestrol (0·3 mg. twice daily) was again given from February 12. In March the blood non-protein nitrogen was 52 mg. per 100 ml., and breast development was beginning. The dose of dienoestrol was increased to 1 mg. twice a day, and thereafter was given for periods of 18 days followed by 10 days without treatment. In May 1947 the patient had an attack of pain in the left loin. A second menstrual bleeding occurred during this month; the blood non-protein nitrogen was now 50 mg. per 100 ml. A further attack of renal colic occurred in December. By March 1947 the patient had gained 12 lb. in weight, and had grown three-quarters of an inch. In 1948 she was able to work as a factory machinist, and in April 1950 she felt so well that she stopped treatment of her own accord; she failed to attend again until September 1951. Then, at the age of 23 years, she weighed 5 st. 7 lb., and had normal spontaneous menstruation. Radiological examination showed increased growth of the large staghorn calculus, but there was an improvement in the nephrocalcinosis. In September 1951 she was admitted to the Bristol Royal Infirmary under the care of one of us (C. B. P.). Her physical deformities were conspicuous (Plate 16, Fig. 3). She was then found to have a moderate degree of acidosis, the plasma-bicarbonate being 20·5 mEq. and the plasma-chloride 112 mEq. per litre, with a low serum-potassium level of 3·3 mEq. per litre. She was treated with a mixture containing citric acid 4 gm., sodium citrate 4 gm., and potassium citrate 4 gm., which was taken three times a day; the acidosis was thereby corrected. In March 1954, when she was last seen, she weighed 6 st. 10 lb.; she had normal female development, and was a lively, happy person, able to work regularly. Radiologically there was progressive disappearance of the nephrocalcinosis, but the large staghorn calculus was increasing in size, and there was a long chain of calculi in the left ureter.

Case 4. A brother of the preceding patient (Case 3), aged 14 years, in February 1953 while attending the hospital with his sister, complained of attacks of pain in his left loin. Similar attacks of pain had occurred since childhood. At birth he had weighed 9 lb. 8 oz., and he had had no serious illnesses. He always passed large quantities of urine and drank a lot of fluids. It was noticed by his mother that he was not growing and was, in fact, not so tall as his younger brother. On examination in 1953 he was very small, but normally proportioned. Radiologically there was retardation of epiphyseal development, with only seven small carpal bones and an apparent bone age of less than nine years. In July he was admitted to the Bristol Royal Infirmary under the care of one of us (C. B. P.). He had recently broken his ankle playing football. Biochemical changes typical of renal tubular acidosis were present, the serum-sodium being 145 mEq. per litre, the serum-potassium 3·1 mEq., the plasma-chloride 110 mEq., the plasma-bicarbonate 18 mEq., and the plasma-phosphate 1·9 mEq. per litre. A water-dilution test after 700 ml. of water produced a urine of specific gravity 1,003 and a profuse diuresis, 1,175 ml. of urine being passed in four hours. A

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urine concentration test produced a urine of maximum specific gravity of 1,008, with a tendency to polyuria. The urine was alkaline, contained a trace of protein, and on microscopy contained no casts and 3·5 white blood-cells per high-power field. Culture of the urine remained sterile. A 24-hour specimen of urine contained 3·8 mg. aminoacid nitrogen per 100 ml., with a normal pattern on chromatography. The electrocardiogram was normal. The patient was treated with a mixture containing 1·5 gm. potassium citrate, 1·5 gm. sodium citrate, and 1·5 gm. citric acid, which he took three times a day; this mixture restored the blood electrolytes to normal, the serum-sodium being 142 mEq., serum-potassium 4·1 mEq., plasma-chloride 104 mEq., plasma-bicarbonate 25·5 mEq., and plasma inorganic phosphate 2·8 mEq. per litre.

The father of these two patients (Cases 3 and 4) was found on radiological examination to have renal calculi. Except for a rather low plasma-bicarbonate level and a urine of pH 6·8, no gross biochemical abnormalities were found.

Case 5. A woman aged 45 years was apparently well until 1952, when in February she developed pneumonia. Recovery was very slow, and she was in hospital and a convalescent home for 13 weeks. She did not receive a sulphonamide. During her convalescence she found difficulty in walking and stumbled, and sought medical advice on several occasions. In December 1952 she was described as having 'indefinite illnesses' and her 'make-up was that of a mild depressive'. No abnormality was found on physical examination, and no diagnosis was made. In February 1953 she was admitted to a hospital complaining of weakness in all her limbs, and of lack of energy for the preceding year. She was found to have bronchitis, and was considered to be 'asthenic'. In April 1954 it was noted that she was 'never able to put on weight'. but on examination no abnormality was found, and her symptoms were considered to be of psychological origin. In July 1954 she was admitted to the Royal South Hants Hospital under the care of Dr. K. M. Robertson. She was complaining of pain in the back of her neck, which was relieved by resting her head or by supporting it with her hand. She described three 'attacks', occurring at intervals of about a year, in which she was unable to move her arms, legs, and neck.

On examination the patient was a somewhat frail woman of average stature. Her speech was slurred, and it was noticed that she had difficulty in keeping her jaws closed. The right biceps-jerk, the supinator-jerks, and the ankle-jerks were absent. Her limbs were flaccid and her arms weak, and she was unable to dorsiflex her feet. The pulse was irregular, with extrasystoles. The heart, chest, and abdomen were normal. On July 6 the serum-potassium was 2·6 mEq. per litre. On July 9 the plasma-sodium was 134 mEq., plasma-potassium 2·9 mEq., plasma-chloride 117 mEq., plasma-bicarbonate 17·8 mEq., and plasma inorganic phosphate 0·9 mEq. per litre. The total serum-calcium was 4·8 mEq. per litre. The urine was alkaline; it contained a trace of protein, and the deposit a fair number of leucocytes and an occasional red blood-cell. On culture it was sterile. A plain radiograph of the abdomen showed multiple small calcified spots throughout both kidneys. An intravenous pyelogram confirmed the fact that the areas of calcification lay within the kidneys. Concentration of dye was poor, and the right kidney appeared to be somewhat enlarged. The urea clearance was 70 per cent. of normal, and blood-urea 17 mg. per 100 ml. A urine concentration test gave a urine of maximum specific gravity of 1,010.

The patient was treated with a mixture containing potassium citrate 1 gm. and sodium bicarbonate 1 gm. three times a day. When she was discharged the serum-potassium had risen to 3·9 mEq., the plasma-sodium to 146 mEq., and

the plasma inorganic phosphate to 2·9 mEq. per litre, while the plasma-bicarbonate was 24 mEq. per litre. The muscular weakness had disappeared, the patient's mental outlook had improved, and the tendon-reflexes had returned to normal. The electrocardiogram, which originally showed auricular extrasystoles and changes in the S–T segment, was now normal.

Discussion

Little is known about the nature of renal tubular acidosis, neither its cause nor the mechanism of the tubular defect being understood. That the disorder is found in infants and has been reported in twins (Rendle-Short, 1953) suggests a congenital abnormality, akin to the de Toni–Fanconi syndrome, idiopathic hypercalcuria, cystinosis, and renal glycosuria. Many of the reported cases have been fatal (Lightwood, 1935; Anderson, 1939; Butler, Wilson, and Farber, 1936; Peterman, 1945; MacGregor, 1948; Boutourline-Young, 1949; Rendle-Short, 1953); but apparent recoveries have been described (Doxiadis, 1952), a possible explanation being that such patients have suffered merely from a retarded development of normal renal function. The aetiology of the syndrome in older children and adults is even less clear. It is possible that these patients are survivors from the infantile group who failed to recover; or they may be suffering from some acquired and therefore aetiologically distinct disorder. Two of our five patients (Cases 1 and 3) were clearly abnormal from the earliest age, and two (Cases 3 and 4) were sister and brother. A congenital, and at least sometimes familial, disorder seems probable. A familial incidence has been reported previously by Schreiner, Smith, and Kyle (1953). Two of our patients, however, were much older at the time of most of their symptoms, being 26 (Case 2) and 43 (Case 5) years of age. Can it be supposed that they, too, were suffering from a congenital disorder? It is clear that there may be all degrees of severity of renal tubular acidosis. The father of two of our patients (Cases 3 and 4), who is not included in the series, was found, during a survey of the family, to have some renal calcification; the plasma-bicarbonate level was low, and the urinary pH rather high at 6·8. In the family described by Schreiner, Smith, and Kyle (1953) the patient was 20 years of age before his first symptom —an attack of haematuria—and was not further troubled for another eight years. The patient's son and brother were affected, and the authors mentioned that there was some evidence of the disorder in other members of the family, although renal calcification was not present. It seems, then, reasonable to suppose that all the older patients are suffering from a congenital disorder; whether that condition is identical with the infantile syndrome is uncertain, but there seem to be no clinical distinctions between the two groups to suggest that the disorders are different.

Other explanations have, however, been offered. Peterman (1945) suggested that the syndrome arose as the result of prolonged pyelonephritis. In Case 2 a urinary infection was present, but is more likely to have been a complication of the extensive renal calcification than the cause of the disorder. The disorder in infants is hardly likely to have been caused by prolonged pyelonephritis. Moreover, chronic pyelonephritis is a common disease (Fishberg, 1954), while

renal tubular acidosis in older patients is very rare. Greenspan (1949) suggested that the defect was caused by poisoning of the carbonic anhydrase of the kidney by sulphanilamide. Lightwood, Maclagan, and Williams (1936), however, described the infantile syndrome before the sulphonamides were in general use. One of our patients (Case 5), who developed her symptoms while convalescent from pneumonia, had not been treated with sulphonamide.

It is agreed that the defect lies in the kidney, but its site and nature remain in doubt. The primary abnormality is an inability to produce an acid urine, the other features of the disorder arising as a consequence. Fixed base from the body's stores is used in the excretion of acid metabolites, and there arises an acidosis characterized by high plasma-chloride, low plasma-bicarbonate, and low plasma-phosphate levels. The urinary output of ammonia is lower than that found in other types of acidosis. Loss of calcium leads to the development of rickets, and loss of potassium to muscular weakness. Albright, Consolazio, Coombs, Sulkowitch, and Talbott (1940) suggested that the urinary loss of calcium leads to a low serum-calcium level. To counteract the decrease of serum-calcium the parathyroid glands hypertrophy, and produce hypophosphataemia. Govan (1950), however, in a detailed post-mortem examination of a fatal case, found no evidence of parathyroid hyperplasia. The renal calcification is considered to be due to the decreased solubility of calcium in an alkaline medium, and to be purely a consequence of the renal defect. Indeed Albright, Burnett, Parson, Reifenstein, and Roos (1946) have shown that in renal tubular acidosis calcification may be absent or may take the form of nephrolithiasis or nephrocalcinosis, or both.

Acidification of the urine and renal production of ammonia. In the presence of an acidosis the normal kidney increases the acidity of the urine and its content of ammonium. Acidification of the urine and the formation of ammonia are a function of the distal tubules, and it is generally agreed that acidification of the urine is achieved by an exchange of sodium for hydrogen ions. Thereby base is spared. Sartorius, Roemmelt, and Pitts (1949) believed that acidification of the urine is controlled by the amount of bicarbonate reaching the distal tubules. Normally the hydrogen ions, exchanged for sodium ions, react with bicarbonate to form carbonic acid. In consequence the urine is only slightly acid. In acidosis the blood-bicarbonate, and hence the bicarbonate of the glomerular filtrate, are decreased, a relatively greater amount is reabsorbed in the proximal tubules, and little or none reaches the distal tubules. Hydrogen ions now react with phosphate and other buffers, with the formation of acid phosphate and an increased acidity of the urine. Other factors, however, must play a part in acidification of the urine. Hendrix and Sanders (1923), on infusing alkaline sodium phosphate into slightly acidotic dogs, found an increase of bicarbonate in the blood, but an increase in urinary acidity and in ammonium content. Schwartz, Jenson, and Relman (1955) administered infusions containing both sodium sulphate and bicarbonate to subjects previously prepared in such a way that they would retain sodium. No change in blood pH or serum carbon dioxide occurred. The urine, on the other hand, became markedly

acid, and ammonium excretion increased. In normal controls no change in the urine was found. The acidification of the urine was attributed to retention of sodium.

The normal subject excretes in the urine about 30 to 50 mEq. of ammonium daily, the amount being greatly increased in the presence of an acidosis. Ammonia is produced in the cells of the distal tubules largely through the action of the enzyme glutaminase on the aminoacid glutamine. When the tubular urine is alkaline there is little tendency for ammonia to diffuse into it, and the ammonia probably escapes into the blood-stream, to be converted into urea in the liver. When the urine is acid ammonia diffuses into it readily, there to be converted into ammonium and neutralized by the acid radicles responsible for the acidosis. Other factors, however, are involved, for there may in some circumstances be a discrepancy between the pH of the urine and the quantity of ammonium excreted. In renal tubular acidosis the urine is alkaline or only weakly acid, and the urinary excretion of ammonium is less than in other forms of acidosis of similar severity. That there is no intrinsic defect in the mechanism of acidification of the urine and the renal production of ammonia is shown by the work of Latner and Burnard (1950), who found that infusions of phosphate given to patients with the infantile form of the disease caused the urine to become more acid and its ammonium content to rise. From their observations they argued that in renal tubular acidosis there was a defect in reabsorption of bicarbonate in the proximal renal tubules. That there is a defect in the function of the renal tubules in this disorder seems undoubted, but at the present time a complete explanation of its nature is not possible.

Potassium depletion and renal function. The production of a copious urine, with its specific gravity fixed at about 1,010, appears to be a natural feature of renal tubular acidosis. There is, however, evidence that renal function is depressed in the presence of potassium deficiency. Schwartz and Relman (1953) described two patients who developed a severe deficit of potassium following excessive use of laxatives. In both patients the ability of the kidneys to produce a concentrated urine was impaired, and clearance tests showed reduction, considerable in one subject, in glomerular and tubular function. On correction of the potassium deficiency there was a return of renal function to normal. It is therefore of interest that in our first patient, in 1941, at a time when she was experiencing attacks of muscular weakness, the blood non-protein nitrogen was 48 mg. per 100 ml., and a urinary dilution test yielded a urine of minimum specific gravity of 1,008. In June 1950, when her serum-potassium was below normal, the minimum specific gravity during dilution tests was 1,005 to 1,006. After correction of the potassium deficiency the administration of two pints of water produced a prompt diuresis, with a urinary specific gravity of 1,002. The blood non-protein nitrogen was now normal. Our third patient in September 1951 had a serum-potassium level of 3·3 mEq. per litre, and the non-protein nitrogen was 50 mg. per 100 ml. After treatment with sodium and potassium citrates the potassium level became normal, and in December 1951 the non-protein nitrogen was 26 mg. per 100 ml. and thereafter remained normal. The possibility

that dehydration may have played a part in the azotaemia cannot, perhaps, be excluded, but as the patients were able to drink freely it seems a less likely explanation.

On the other hand there is evidence that long-standing potassium deficiency may itself lead to organic changes in the kidney. Schrader, Prickett, and Salmon (1937) described, in rats maintained on potassium-deficient diets, a 'diffuse tubular nephritis', the tubular epithelium being oedematous and vacuolated and sometimes sloughing. Follis, Orent-Keiles, and McCollum (1942) found lipid changes in the cells of the convoluted tubules in similarly treated rats. Some tubular cells were necrotic. They also noted dilated tubules lined by degenerated and flattened epithelium, and occasional calcification of epithelial cells. Keye (1952) has described vacuolation of epithelium, particularly in the proximal convoluted tubules, of the kidneys of a patient who died in potassium deficiency resulting from steatorrhoea. Whether potassium deficiency, by producing organic renal changes, leads to further depression of renal function in tubular acidosis, or whether it plays any part in producing nephrocalcinosis, a possibility hinted at by the work of Follis, Orent-Keiles, and McCollum, is unknown. These considerations perhaps lend added weight to the importance of correction of potassium deficiency in these patients.

Incidence and diagnosis. Renal tubular acidosis in older children and adults is extremely rare. Pines and Mudge (1951) were able to collect only 14 cases from previous reports, and added three of their own. The fact that we have found five cases since 1946 suggests that the disorder may be more common than is apparent. The diagnosis of renal tubular acidosis depends essentially on the biochemical finding of a hyperchloraemic hypophosphataemic acidosis with an alkaline or only slightly acid urine. The disorder must be differentiated from the Fanconi syndrome, in which there is a similar acidosis together with glycosuria and aminoaciduria. The similarity and differences between renal tubular acidosis and the Fanconi syndrome have been discussed by Milne, Stanbury, and Thomson (1952.) On clinical grounds the diagnosis of renal tubular acidosis can only be suspected; biochemical tests are essential for its confirmation. In milder cases, and perhaps for years in more severe examples, symptoms may be absent. None of the symptoms is specific for the disease. When present, the symptoms are variable from patient to patient, and even in the same patient at different times. The diagnosis is therefore not easy to make. Of our five patients, one (Case 1) was for some years diagnosed as suffering from renal rickets; Case 2 was at first accepted as a simple case of renal stone; Case 4 was found during a survey of the previous patient's family; and another patient (Case 5) was repeatedly considered to be hysterical. The diagnosis may be considered in the following circumstances:

1. The presence of rickety changes, which may vary in severity from easily produced fractures to severe bony deformity.

2. The presence of attacks of muscular weakness, trivial or severe. The patient's description may be very vague, and he may speak of ill-defined

weakness, some difficulty in walking, or episodes of 'collapse'. One or two of our patients have described 'stiffness' of their muscles, which on one occasion led to an erroneous diagnosis of tetany.

3. The presence of renal colic, haematuria, the passage of stones *per urethram*, pain in the loins, repeated attacks of renal infection, polyuria, and thirst, and perhaps pyuria. In these circumstances the radiological finding of nephrocalcinosis, while not diagnostic of the disease and indeed not always present, is a helpful pointer to the diagnosis.

Whenever a patient is shown to have renal tubular acidosis, an examination of his relatives may reveal the disorder among them.

Treatment. The aim of treatment is to supply the patients with extra base, in order to enable them to excrete acid metabolites in neutral form without drawing upon the body's stores of base. This aim is achieved by giving alkalinizing salts such as sodium citrate, potassium citrate, and sodium bicarbonate. This symptomatic treatment has been very successful. Albright, Burnett, Parson, Reifenstein, and Roos (1946) advocated that, in order to heal the rickets in the shortest possible time, massive doses of calciferol and a high-calcium diet should be given in addition to sodium citrate. They pointed out that the patient will then be in positive calcium balance, although such therapy will cause a large loss of calcium in the urine. In 1946 our third patient was so treated, with healing of her rickets. We have already referred to the marked tendency of patients with renal tubular acidosis to develop renal calcification, a tendency attributed to the alkalinity of their urine and to the insolubility of calcium salts in alkaline solutions. It therefore seems to us undesirable to employ any measure which involves an increased urinary excretion of calcium. Moreover even in normal subjects large doses of calciferol may lead to renal calcification. We have not in recent years had experience in treating patients suffering from renal tubular acidosis with gross active rickets. In March 1941 our first patient had undoubted rickets; in October 1941, after treatment with sodium citrate and sodium bicarbonate alone, radiological examination showed the rickets to be healed. In 1950 no evidence of rickets was found. We therefore feel that, at least where the rickety changes are not gross, treatment with alkalinizing salts is adequate, and that the use of calciferol should be avoided.

In all our patients we have used varying combinations of sodium citrate, potassium citrate, and sodium bicarbonate, the total amount ranging from 2 to 8 gm. three times a day. In our second patient potassium citrate caused a mild alkalosis, without entirely correcting the potassium deficiency; the addition of potassium chloride restored the level of potassium to normal. In each case the combinations of alkalinizing salts have been varied from time to time, the aim, which was achieved, being to restore the blood electrolytes to normal. The improvement in physical well-being of all our patients has been gratifying. Our first patient, who was under-weight before treatment, gained weight rapidly when the acidosis was corrected, an observation which suggests that there may be a profound disturbance of metabolism in the presence of a

prolonged and severe acidosis. Our second patient was unfortunate in that the urinary infection, which complicated renal calcification, could not be eradicated and continued to be troublesome.

The danger of sulphonamides. We wish to emphasize the danger of administering sulphonamides to patients with renal tubular acidosis. Many sulphonamides, including sulphanilamide, sulphathiazole, sulphadiazine, sulphamezathine, and the diuretic agent diamox, inhibit in varying degree the enzyme carbonic anhydrase, which plays a part in the acidification of the urine (Miller, Dessert, and Roblin, 1950). In the normal dog diamox causes an increased urinary excretion of bicarbonate, sodium, potassium, and water, together with an acidosis and sometimes an increase of the plasma-chloride (Maren, Wadsworth, Yale, and Alonso, 1954). These are the very abnormalities that appear to be present in renal tubular acidosis. The patient of Baines, Barclay, and Cooke (1945) died after taking sulphathiazole, and our second patient nearly lost her life through being given sulphonamides. Sulphonamides, we feel, should never be given to patients with renal tubular acidosis. As we ourselves know, it is easy to forget, and we think that the patients themselves should be emphatically warned not to allow their doctors to give them sulphonamides.

The prognosis is not known. Untreated, the patients may die of potassium deficiency, and in the absence of treatment renal calcification is presumably progressive, and must sooner or later lead to extensive renal damage. When the acidosis is corrected there seems to be no reason why the patients should not remain in good health for many years. We were, however, disappointed to find that in Case 1, in spite of excellent electrolytic control, the nephrocalcinosis tended to increase (Plate 15, Fig. 2). Damage to the kidney by calcium deposition, and the possible superimposition of infection, appear to be the main hazards in the treated patient. On these grounds alone early diagnosis and treatment seem most desirable.

We gratefully express our thanks to Dr. K. M. Robertson for permission to publish Case 5; to Dr. R. C. Clarke for permission to use the notes of the admission of Case 3 in 1946; to Dr. G. A. Smart for his help with Case 1; to Dr. G. K. McGowan and Mr. F. C. Grimes for the biochemical analyses; and to Mr. Godden, of the Department of Medical Photography, University of Bristol, for the photographs.

Summary

The clinical, biochemical, and radiological features, and the treatment in five new cases of renal tubular acidosis in older children and adults, are described. The danger of administering sulphonamides to these patients is stressed. A familial incidence is reported, and arguments are brought forward to suggest that the disorder is a congenital defect of renal function.

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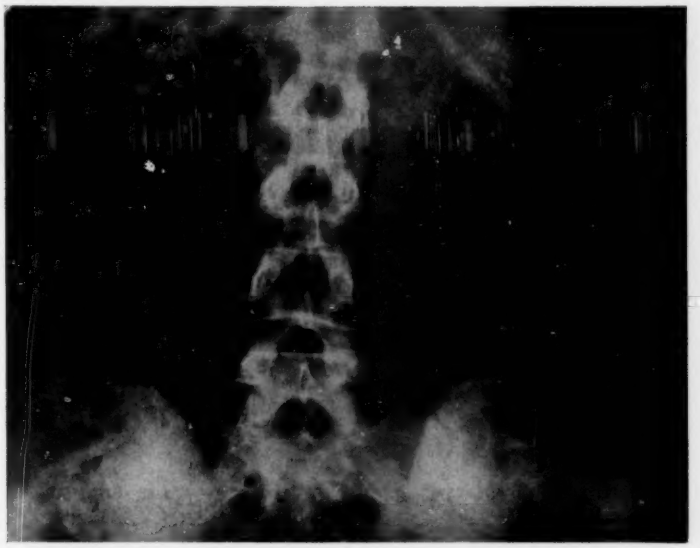

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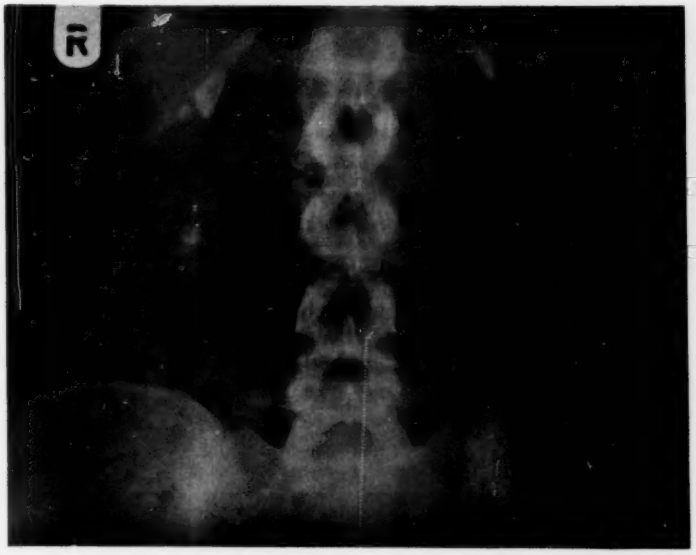

(*b*)

FIG. 2. X-rays of Case 1, (*a*) in 1951; (*b*) in 1955, showing the progress of the nephrocalcinosis

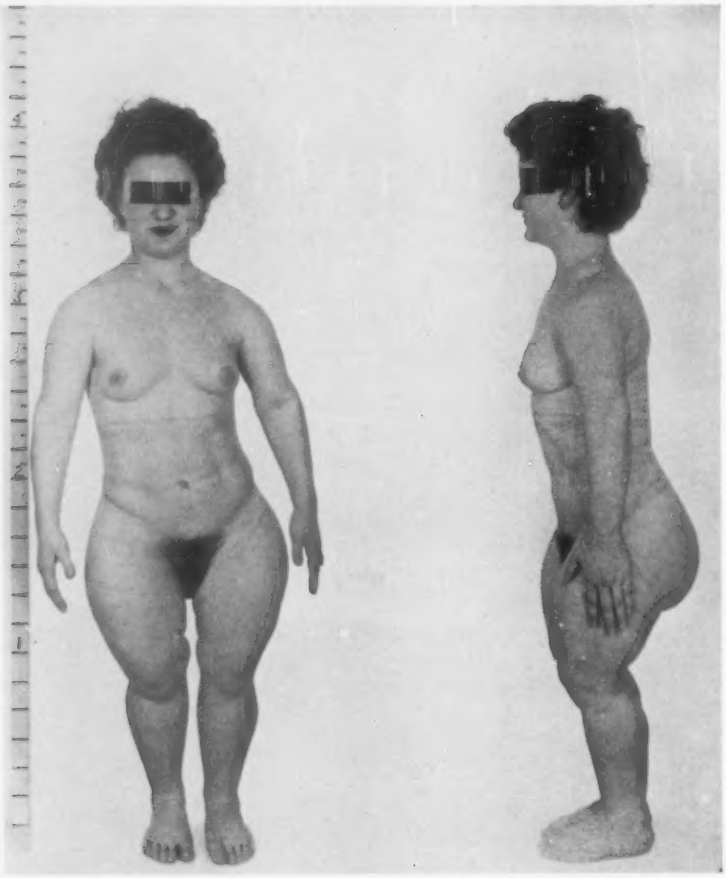

FIG. 3. Case 3. The patient in 1951, at the age of 23 years

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HAEMATOGENOUS BRAIN ABSCESS IN CYANOTIC CONGENITAL HEART DISEASE[1]

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With Plates 17 and 18

THE suggestion of Ballet (1880), that a cardiac malformation sometimes predisposes to the development of a brain abscess, is supported by a significantly large number of published cases of association of the two lesions. In the majority of these cases the abscess was not due to continuous spread of an inflammatory process from a contiguous source, such as cranial osteomyelitis, otitis media, or paranasal sinusitis; nor was it a complication of cranial injury. Infection appears, therefore, to have been blood-borne in most instances, and only the occurrence of haematogenous brain abscess in congenital heart disease will be considered in this paper. Since January 1944 seven patients with solitary haematogenous brain abscess and cyanotic congenital heart disease have been treated in the United Birmingham Hospitals. These cases are described in some detail in order to facilitate diagnosis of the intracranial complication. Their pathological features are analysed in conjunction with 72 previously reported cases of haematogenous brain abscess in congenital heart disease, and treatment is discussed. The abscesses were usually solitary in the brain; they were not the result of bacterial endocarditis, except possibly in a very small minority of cases; and they were not due to bronchiectasis, lung abscess, or empyema thoracis. Suppuration was seldom present elsewhere in the body, and in most cases the source of infection was not discovered. Thus only a few of the abscesses were undoubted metastatic infections. It is possible that others were true primary brain abscesses, due to organisms which entered the blood-stream without producing an inflammatory reaction at their site of invasion of the body. The associated cardiac malformations were of many kinds, Fallot's tetralogy predominating, but almost invariably belonged to the cyanotic group. It may be concluded, therefore, that a central venous-arterial shunt predisposes to the development of a haematogenous brain abscess.

Case Reports

Case 1. Fallot's tetralogy; temporoparietal brain abscess.

A. D., aged 14 years, was admitted to hospital under the care of Dr. E. Bulmer on September 20, 1945, with a left-sided headache of five days' duration. She was known to have congenital heart disease, but had been otherwise well till

[1] Received August 25, 1955.

a week before the onset of headache, when she developed a cold and sore throat. The day after the headache began the right side of the face was noticed to be weak, and the right hand to be clumsy. Examination on admission showed a right hemiparesis, most evident in the face, with an extensor plantar response on the affected side. There was moderate stiffness of the neck, and a positive Kernig's sign. Some purpuric spots were noticed on the left forearm. The heart was not enlarged, but a systolic thrill and a harsh systolic murmur were present over the precordium and most intense in the pulmonary valve area. Her pulse-rate was 90 per minute, and her temperature rose to 101° F. soon after admission. The blood leucocyte count was 11,150 per c.mm. (89 per cent. polymorphonuclear). *Staph. aureus* and β-haemolytic streptococci were present in the nose. It was thought that she had a left frontal suppurative encephalitis secondary to frontal sinusitis. On systemic penicillin therapy her fever subsided, but she became drowsy and dysphasic, and the hemiparesis worsened. By September 29 she was irrational, and had marked rigidity of the neck and early papilloedema. Lumbar puncture revealed very turbid fluid under 400 mm. pressure. She died next day, and examination of the brain disclosed a large left temporoparietal abscess, which had ruptured into the ventricular system. There was no frontal sinusitis, and the only other positive finding at autopsy was the tetralogy of Fallot.

Case 2. Fallot's tetralogy; abscess of brain stem.

E. J., aged 16 years, was known to have a congenital cardiac lesion, and was usually somewhat cyanotic. Early in February 1947 he developed bronchitis, with considerable cyanosis, but had recovered from this illness when, on March 3, he complained of headache. On March 7 right facial weakness and a dilated left pupil were noted. Next day he was admitted to hospital under the care of Dr. A. V. Neale. He was drowsy, and extremely dysarthric. Finger clubbing, cyanosis, and rigidity of the neck were present. There was no papilloedema, but he had a complete third cranial nerve palsy on the left side, paralysis of the lower right cranial nerves from the sixth to the 12th inclusive, and a spastic right hemiparesis with a right extensor plantar response. Later in the day both plantar responses were extensor. There was a precordial systolic thrill, and a systolic murmur best heard in the third left intercostal space near the sternum. Blood examination showed 7,800,000 erythrocytes per c.mm., 21·8 gm. haemoglobin per 100 ml., and 9,300 leucocytes per c.mm. Lumbar puncture revealed clear colourless fluid, under 140 mm. pressure, which contained 16 leucocytes per c.mm. (mostly lymphocytes), and 68 mg. sugar, 70 mg. protein, and 725 mg. chloride per 100 ml. No bacteria were found in the cerebrospinal fluid. He deteriorated steadily, and died on March 11 of central respiratory failure. Penicillin therapy was used only during the last 24 hours. Autopsy revealed the cardiac malformations of Fallot's tetralogy. There was no endocarditis. An abscess was found in the right side of the pons and mid-brain, extending into the right cerebral peduncle and into the right cerebellar hemisphere. The middle-ear cavities and the paranasal sinuses were not infected.

Case 3. Cyanotic congenital heart disease; parietal brain abscess; recovery, but sudden death two years later.

M. W. was occasionally cyanotic from the age of 12 months, and easily tired on exertion. At the age of 17 years, after feeling vaguely unwell for two days, she developed a persistent severe headache, which was mainly on the left side and was associated with vomiting. Three days after the headache began she complained of blurred vision, and two days later, on November 23, 1949, she

was admitted under the care of Dr. D. R. Humphreys. On examination she was drowsy and cyanotic, with marked nuchal rigidity and a positive Kernig's sign. No other neurological abnormality was detected. Her temperature was 100·8° F., and pulse-rate 110 per minute. A rough systolic murmur was audible all over the heart, but was loudest at the sternal end of the fourth left intercostal space. Lumbar puncture revealed turbid fluid under high pressure; it contained 17,000 leucocytes per c.mm. (98 per cent. polymorphonuclear), and 710 mg. chloride and 13 mg. sugar per 100 ml. No bacteria were demonstrable in this or subsequent specimens of cerebrospinal fluid. Blood investigation showed 6,690,000 erythrocytes per c.mm., 41,800 leucocytes per c.mm. (89 per cent. polymorphonuclear), and 18 gm. haemoglobin per 100 ml. An electrocardiogram showed right ventricular preponderance.

Pyogenic meningitis was diagnosed, and treatment was begun with systemic and intrathecal penicillin and systemic sulphadiazine. She improved at first, and had no pyrexia at the end of a week, but on December 9 vomiting recurred, and a right homonymous hemianopia was found. On December 14 the lumbar cerebrospinal fluid was still under raised pressure, but now contained only 68 leucocytes per c.mm. (all mononuclear). Next day a right hemiparesis was detected after a generalized epileptic fit. There was no evidence of otitis media, paranasal sinusitis, or chest infection. On December 17 parietal cranial burr-holes were made by Mr. J. M. Small, and on passing a cannula into the left parietal lobe of the brain an encapsulated abscess was found. Thirty-five ml. of pus were aspirated, and penicillin and thorotrast were injected into the cavity. Air was introduced into the right lateral ventricle, and subsequent radiographs of the skull (Plate 17, Figs. 1 and 2) showed the position of the abscess and displacement of the right lateral and third ventricles to the right. There was no evidence of other brain abscesses. The pus was sterile on culture, but in smears many Gram-positive cocci, probably degenerate streptococci, were seen.

She made a steady recovery after the initial aspiration of the abscess. Systemic penicillin therapy was continued, and several further aspirations were done during the ensuing six weeks. The abscess, as seen radiologically, finally became a mere scar about 1·5 cm. in diameter. It seemed to be quite inactive, and excision was not considered necessary. She was discharged on February 14, 1950, and remained very well for 18 months. Then cyanosis and dyspnoea began to develop more readily on exertion. Several syncopal attacks occurred, and she died suddenly in one of these attacks in June 1952. No internal post-mortem examination was made.

Comment. The exact nature of this girl's cardiac malformation was not discovered, but she probably had a septal defect associated with a right-to-left shunt. When the brain abscess developed blood cultures were not made, but there was no clinical evidence of bacterial endocarditis, and no history or sign of any other possible source of infection.

Case 4. Functionally univentricular heart; Blalock–Taussig anastomosis; frontal brain abscess.

M. S. had been cyanotic and dyspnoeic from early infancy. In June 1949, when aged five years, he was admitted under the care of Dr. O. Brenner. He was undersized, and exhibited marked digital clubbing, extreme cyanosis, and dyspnoea on slight exertion. The heart was large, the apex beat being palpable in the sixth intercostal space in the anterior axillary line. A systolic precordial thrill and murmur were present. Special cardiac investigations suggested pulmonary stenosis associated with an interventricular septal defect. In July

1949 a Blalock–Taussig anastomosis was performed by Mr. A. L. d'Abreu. After this operation exercise tolerance improved, but the degree of cyanosis remained unchanged.

He was readmitted on November 18, 1951, with a four-day history of severe frontal headache and lassitude. There was no history of respiratory infection, earache, or aural discharge. His pulse-rate was 112 per minute, and temperature 100° F. He had slight stiffness of the neck, and Kernig's sign was positive, but no other neurological abnormality was detected. Blood examination showed 13,600 leucocytes per c.mm. (80 per cent. polymorphonuclear), 7,700,000 erythrocytes per c.mm., and 22·4 gm. haemoglobin per 100 ml. The lumbar cerebrospinal fluid was turbid, under high pressure, and contained over 500 leucocytes per c.mm. (95 per cent. polymorphonuclear). There were 52 mg. protein and 61 mg. sugar per 100 ml. of cerebrospinal fluid, but no bacteria were demonstrable in smears or cultures from it. It was assumed that he had mild meningitis due to bacteriaemia associated with subacute bacterial endocarditis. An intensive course of systemic therapy with sulphadiazine, penicillin, and aureomycin was begun, and maintained throughout the illness. Headache and meningeal irritation disappeared by the end of the first week in hospital, but a low fever persisted for three weeks. Several blood cultures were sterile, and he developed neither anaemia nor embolic phenomena.

On February 10, 1952, fever, headache, and nuchal rigidity returned. Four days later mild papilloedema was noticed, but there were still no other abnormal neurological signs. The lumbar cerebrospinal fluid was again turbid and under high pressure, and contained 6,000 leucocytes per c.mm. (80 per cent. polymorphonuclear), but no demonstrable bacteria. By February 16 he had well-marked papilloedema, and was moribund. Cannulation through frontal cranial burr-holes revealed purulent cerebrospinal fluid in the lateral ventricles, indicating rupture of an abscess into the ventricular system. Intraventricular antibiotic therapy was unavailing, and he died next day. The ventricular cerebrospinal fluid was sterile, but degenerate streptococci and Gram-negative bacilli were seen in stained films prepared from it.

Autopsy (Dr. R. Lannigan). The pulmonary artery lay posterior to the aorta, and both arose from the left ventricle. The circumference of the pulmonary valve was 2 cm.; that of the aortic valve was 5·5 cm. The only exit from the hypertrophied right ventricle was through a defect in the posterior part of the interventricular septum. The atria were normal, and the foramen ovale was closed. The mitral cusps were thickened and distorted, but the other valve-cusps were normal. There was no sign of bacterial endocarditis, but a few small vegetations were visible at the line of the side-to-side anastomosis between the left pulmonary and left subclavian arteries. Microscopically these vegetations were fibrinous, and did not contain bacteria or show evidence of inflammation. Beyond the origin of the left subclavian artery there was a coarctation of the aorta, measuring 1·5 cm. in circumference. The right frontal lobe of the brain contained an encapsulated abscess, 5 cm. in diameter, which had ruptured into the frontal horn of the right lateral ventricle. Foul greenish pus was found in the abscess and throughout the ventricular system. No other abscesses were found in the brain or elsewhere, and there was no sign of embolic infarction anywhere in the body.

Case 5. Fallot's tetralogy; parietal brain abscess.

A. B., an industrial worker aged 36 years, was admitted on April 19, 1952, under the care of Dr. C. F. Hawkins. Severe headache had been present for a fortnight, and a generalized epileptic fit had occurred a few hours after the

headache began. Paralysis and numbness of the right side of the body had been present for a week, coming on gradually in the course of 24 hours, and affecting the arm first. Congenital heart disease had been detected in childhood, and exercise always made him breathless. He had marked digital clubbing, moderate cyanosis, and a soft systolic precordial murmur. There was a severe right hemiparesis, associated with impairment of touch and pain sense, and a right extensor plantar response. Blood investigation revealed 8,660,000 erythrocytes per c.mm., 25·6 gm. haemoglobin per 100 ml., and 10,200 leucocytes per c.mm. (91 per cent. polymorphonuclear). The lumbar cerebrospinal fluid was turbid, under 230 mm. pressure, and contained 370 leucocytes per c.mm. (62 per cent. polymorphonuclear), and 56 mg. sugar, 705 mg. chloride, and 80 mg. protein per 100 ml. No bacteria were seen in smears from the cerebrospinal fluid, but *Staph. albus* was grown from it (probably a contaminant).

After admission he became drowsy, and by April 22 he was stuporose, with a temperature of 101° F. There was no papilloedema, but a cerebral abscess due to subacute bacterial endocarditis was now suspected. Cannulation through a left parietal cranial burr-hole (Mr. E. A. Turner) disclosed a large non-capsulated abscess at 5 cm. depth. After 45 ml. of offensive pus had been aspirated, thorotrast, penicillin, and streptomycin were injected into the abscess cavity. Gram-positive cocci and occasional Gram-negative bacilli were seen in smears of the pus, but it was sterile on culture. The two antibiotics were also administered systemically, and later into the cerebrospinal fluid as well. His level of consciousness rose, and he regained some power in the paralysed limbs, but on May 6 his condition began to deteriorate again. Two days later cerebrospinal fluid escaped when the abscess was aspirated, indicating that it had ruptured into the ventricular system, and this fact was confirmed radiographically (Plate 17, Fig. 3). There was irregular low fever, but blood cultures were sterile. On May 18 the fever ceased, but he was then in semi-coma. Pneumoventriculograms showed that the left lateral ventricle had become shut off from the rest of the ventricular system, and was undergoing progressive enlargement. His condition worsened in spite of the fact that the ventricular infection appeared to be under control, and he died in status epilepticus on June 6.

Autopsy (Dr. W. T. Smith). The paranasal air sinuses and middle-ear cavities were normal. There was herniation of the cingulate gyrus of the left cerebral hemisphere beneath the falx cerebri, due to an enormously dilated left lateral ventricle. The ependyma of this ventricle was thickened, and from its body a small diverticulum projecting upwards was all that remained of the ruptured parietal abscess. Another abscess, 1 cm. in diameter, in the choroid plexus of this ventricle just lateral to, and obstructing, the foramen of Monro, was probably due to direct infection from the ventricle. The heart weighed 340 gm., and showed the features of Fallot's tetralogy. The right ventricle was hypertrophied, and a deficiency of the upper and posterior part of the interventricular septum was straddled by the aorta. The pulmonary artery was only 6 mm. in diameter. There was no evidence of bacterial endocarditis, but the tricuspid and pulmonary valves were thickened and fibrotic. Apart from terminal bronchopneumonia, the lungs showed no sign of recent infection. Pleural adhesions, and calcification at both pulmonary apices, indicated tuberculous infection in the past. There were no other significant abnormalities.

Case 6. Probable Fallot's tetralogy; pulmonary valvulotomy; frontal brain abscess; recovery.

R. F. was investigated when two years old by Dr. Clifford Parsons in October 1949. He had been cyanotic from the age of six weeks, and there was marked

digital clubbing. A harsh precordial systolic murmur was loudest in the pulmonary area, and accompanied by a thrill. Moderate cardiac enlargement was present. An electrocardiogram showed right ventricular preponderance, and angiocardiography indicated a free communication between the right and left sides of the heart. Fallot's tetralogy was diagnosed, and in July 1952 pulmonary valvulotomy was carried out by Mr. d'Abreu. Convalescence was uneventful, exercise tolerance increased, and he was able to attend an ordinary school and play games.

Nearly a year later, on June 6, 1953, he was admitted to hospital with a history of bronchitis two weeks previously, a headache for three days, and a right-sided Jacksonian fit earlier the same day. The fit began in the face, spreading to the arm, then the leg, and was associated with loss of consciousness. The ears, throat, and lungs were normal, but several teeth were carious. Mild cyanosis was present, and the digital clubbing and cardiac signs were virtually unchanged. There was slight stiffness of the neck, Kernig's sign was positive, and the right arm and right side of the face were weak. Blood examination showed 6,700,000 erythrocytes per c.mm., 18·9 gm. haemoglobin per 100 ml., and 11,800 leucocytes per c.mm. (79 per cent. polymorphonuclear). Lumbar puncture revealed clear fluid, under 220 mm. pressure, containing 93 leucocytes per c.mm. (90 per cent. lymphocytes) and 95 mg. protein per 100 ml., but no demonstrable bacteria. Tuberculous meningitis was suspected, and streptomycin therapy was begun, but discontinued after three days when the Mantoux reaction was found to be negative. A blood culture on June 8 was sterile. He improved, and the paresis became less marked, but on June 13 he again complained of headache, vomited, and became drowsy. His blood leucocyte count had risen to 18,800 per c.mm. (90 per cent. polymorphonuclear). On June 15 papilloedema, more marked in the left eye, was noticed. The right hemiparesis had increased, and both plantar responses were extensor. Apart from a single rise of temperature to 100° F. he had had no fever since admission.

A cerebral abscess now seemed likely, and ventriculography through parietal burr-holes showed a large left frontal lesion. Cannulation through a left frontal burr-hole disclosed an abscess at 3 cm. depth, from which 30 ml. of thick, greenish, odourless pus were aspirated. Penicillin and thorotrast were injected into the abscess cavity, and systemic penicillin therapy was commenced. A slowly growing micro-aerophilic streptococcus viridans was obtained by culture from the pus. He had an almost complete right hemiplegia next day, but this soon began to improve. The abscess (Plate 18, Figs. 4 and 5) was treated by aspiration and penicillin replacement, daily at first and then less frequently. It was observed radiologically to become steadily smaller, and finally its cavity was obliterated. All specimens of pus after the first were sterile. Systemic penicillin therapy was maintained for six weeks, because bacterial endocarditis had been suspected. Within a few days of the initial aspiration he was alert and active, being restrained in bed with difficulty. The suspicion of bacterial endocarditis arose merely because of the cerebral abscess, and there was no evidence that this cardiac complication really existed. He was discharged on August 8, 1953, with a mild residual hemiparesis, chiefly in the foot. When last seen in May 1955 he was well, and had almost completely recovered from this paresis.

Case 7. Probable Fallot's tetralogy; Blalock–Taussig anastomosis; parietal brain abscess; recovery.

A. M., who had been a blue baby, was investigated in 1949 when 11 years old. She had digital clubbing, was cyanotic at rest, and easily developed dyspnoea on exertion. A precordial systolic thrill and murmur were present. Radiological

screening and the electrocardiogram supported a diagnosis of Fallot's tetralogy. In October 1949 an end-to-side anastomosis was made between the left subclavian and left pulmonary arteries by Mr. d'Abreu. Exercise tolerance increased, and cyanosis lessened. During May and June 1951 she had haemoptysis on two occasions, and was readmitted. No pulmonary abnormality was detected clinically or radiologically, and blood cultures were sterile. The haemoptyses were attributed to pulmonary hypertension or infarction.

She was next admitted on April 22, 1954, under the care of Professor A. P. Thomson, having had several left-sided sensory fits, starting in the leg, during the previous five days. She had a mild left hemiparesis, and a temperature of 100·2° F. There was slight cyanosis at rest, and digital clubbing had become less marked. Blood examination showed 18·4 gm. haemoglobin per 100 ml., 6,140,000 erythrocytes per c.mm., and 9,900 leucocytes per c.mm. (73 per cent. polymorphonuclear). After admission she had several motor fits involving the left limbs, and on April 25 she complained of headache for the first time, and vomited. Her hemiparesis increased, and papilloedema developed. The lumbar cerebrospinal fluid was under 400 mm. pressure on April 28, but was otherwise normal. On April 30 there was marked weakness of the left arm and leg, most evident in the foot. Tone was increased in the left lower limb, and to a less extent in the right. The left plantar response was equivocal, while the right was flexor, and the left abdominal reflexes were depressed. There was impairment of stereognosis and tactile discrimination in the left hand, and considerable diminution of joint sense in the left foot.

A right parietal brain abscess seemed likely, and parietal burr-holes were made on May 1. Cerebral tension was moderately raised. On the right the parietal lobe felt unusually soft, and the lateral ventricle could not be found with an exploring cannula. The left lateral ventricle was found easily, and cerebrospinal fluid was replaced by air. Subsequent ventriculograms showed a marked shift due to the presence of a right parietal lesion. A further burr-hole was made over this lesion, but again only softened brain was encountered. The cortical veins seen had not undergone thrombosis. It was concluded that the lesion was either pre-suppurative bacterial encephalitis or a sterile infarct. Systemic penicillin therapy had been begun on April 26, and was continued. Headache disappeared, and the neurological signs became less marked. The only possible source of infection found was a large carious cavity in an upper molar tooth. On May 3 the blood leucocyte count had risen to 14,700 per c.mm. (78 per cent. polymorphonuclear). An electroencephalogram showed diffuse abnormality and a focus in the right parietal area. Since admission she had had virtually no fever, but after May 5 there was an occasional elevation of temperature to 100° F. Several blood cultures were negative. Her papilloedema, meanwhile, had been steadily increasing, and headache returned. On May 21 the right parietal lobe was again explored through a burr-hole, and this time an unencapsulated abscess containing 14 ml. of pus was aspirated. No bacteria were found in the pus. Radiographs showed the abscess to be bilocular, the posterior loculus appearing to be the older one (Plate 18, Figs. 6 and 7). The abscess responded well to further aspirations and penicillin replacement, and she was sent home, with a very slight left hemiparesis, on June 27. When seen in January 1955 she was well, and had begun work. There was no clinical or radiological evidence of activity in the abscess scar.

Comment. It seems likely that the posterior loculus of the abscess was present at the time of the original exploration of the right parietal lobe, but was not found because it was then very small.

Incidence of Congenital Heart Disease in Cases of Haematogenous Brain Abscess

Sixty-nine patients suffering from haematogenous brain abscess were treated in the United Birmingham Hospitals during the 10-year period 1944 to 1953 inclusive. Congenital heart disease was present in seven (10·1 per cent.), of whom six are the first six patients reported in this paper, and the seventh was a man of 40 years, with a patent interventricular septum, who had subacute

TABLE I

Aetiological Classification of 69 Cases of Haematogenous Brain Abscess occurring in Birmingham, compared with the Mayo Clinic Series of Gates, Kernohan, and Craig (1950)

Primary infection	*Birmingham series*	*Mayo Clinic series*
1. Bronchiectasis, lung abscess, or empyema thoracis	35	42
2. Bacterial endocarditis		
(*a*) with cardiac malformation	1	0
(*b*) without cardiac malformation	5	15
3. Other primary infections		
(*a*) with cardiac malformation	3	2
(*b*) without cardiac malformation	13	30
4. No known primary infection		
(*a*) with cardiac malformation	3	1
(*b*) without cardiac malformation	9	14
Total	69	104

Note: no patient in Group 1 had congenital heart disease.

bacterial endocarditis and a small terminal brain abscess which was not the cause of death. The 69 cases of haematogenous brain abscess are analysed in Table I, and compared there with the autopsy series reported from the Mayo Clinic by Gates, Kernohan, and Craig (1950). According to Macmahon, McKeown, and Record (1953) the incidence of congenital heart disease in Birmingham is approximately three per 1,000 live births, and, since only one in three of the children affected reaches the age of 10 years, it can be assumed that the incidence of congenital heart disease in the general population is less than 0·1 per cent. Thus the incidence of congenital heart disease in cases of haematogenous brain abscess is very considerably higher than the incidence of congenital heart disease in the general population.

Incidence of Haematogenous Brain Abscess in Patients with Congenital Heart Disease

Abbott (1936) included only seven cases of haematogenous brain abscess in her analysis of 1,000 fatal cases of congenital heart disease, but this large group was not a continuous series, and the brain was not examined in every case. Robbins (1945) found three cases of haematogenous brain abscess in 53 fatal cases of congenital heart disease of all types (5·7 per cent.); Gates, Rogers, and Edwards (1947) found five in 115 (4·3 per cent.). Maronde (1950) found 11 cases

TABLE II

Reported Cases of Haematogenous Brain Abscess in Congenital Heart Disease

No.	Author and year	Sex	Age (years)	Cardiac anomaly	Cyanosis	Digital clubbing	Meningeal reaction	Site of abscess	Organism	Primary focus
1	Farre (1814)	M	9	T of F	+	..	..	R. cerebral hemisphere	..	..
2	Lallemand (1823)	F	57	PS and PFO	+	..	..	R. frontal	..	..
3	Berthody (1845)	F	21	T of F	+	..	..	L. occipital	..	..
4	Ballet (1880)	M	15	Both atria opened into L. ventricle; IVSD	..	..	..	R. fronto-parietal	..	..
5	Burresi (1880)	M	13	PS and IVSD	+	..	..	L. fronto-parietal	..	Septic L. hand 3 months previously
6	Stone (1882)	F	19	PS and IVSD	+	..	..	R. occipital	..	..
7	Acker (1895)	F	10	Transposition of great vessels; pulmonary atresia; PFO; IVSD	+	+	..	R. temporal	Diplococcus lanceolatus	..
8	Jacobi (1895)	M	29	IVSD; small aorta	+	+	+	L. temporal	..	..
9	Deneke (1906)	M	18	Transposition of great vessels; PDA; IVSD	+	+	..	R. cerebral hemisphere	Streptococci	..
10	Heigel (1913)	F	10	Ebstein's malformation of tricuspid; PFO	..	..	..	L. frontal	..	..
11	Abbott, Lewis, and Beattie (1923)	M	11	T of F, but pulmonary atresia; PDA	+	+	+	L. frontal	Streptococci in CSF	..
12	Raab (1923)	M	15	T of F; PFO	+	+	..	R. cerebral hemisphere	..	..
13	Bach (1928)	M	30	Aorta from R. ventricle; pulmonary atresia; IVSD; PFO	+	+	+	R. temporal	Gram-positive bacillus in CSF	Carious teeth extracted 5 days previously
14	Baumgartner and Abbott (1929)	M	20	Eisenmenger complex	+	..	+	R. fronto-parietal	Haemolytic streptococci	..
15	Evans (1931)	F	17	PFO; IVSD	..	..	..	R. occipital	..	..
16	Rabinowitz, Weinstein, and Marcus (1931–2)	F	16	Transposition of great vessels; PS; IASD; and IVSD	+	..	+	Cerebellum	Bact. coli	..
17	Sterling (1934)	F	12	PFO	+	..	+	R. frontal	..	..
18	Ingham (1938)	F	39	PFO	+	+	..	L. temporo-parietal	..	Acute upper respiratory infection 4 days before first symptom of abscess
19	Drey, Strauss, and Gray (1938)	F	14	Functional cor biatriatum triloculare	+	+	+	R. cerebral hemisphere, presumably paraventricular	..	..
20	Wechsler and Kaplan (1940)	M	14	Probable T of F	+	+	..	R. parietal	Gram-negative bacilli and diplococci	Influenza 6 weeks before first symptom of abscess
21	,,	F	11	Probable T of F	+	+	..	R. fronto-parietal	Streptococcus viridans	Bronchitis 3 months previously
22	Hanna (1941)	F	18	IVSD	..	..	+	L. thalamus	..	..
23	,,	F	34	IVSD	..	..	+	L. frontal	Haemophilus influenzae	..
24	,,	M	3	T of F	+	+	+	R. temporal	..	..

T of F = tetralogy of Fallot. PS = pulmonary stenosis. PFO = patent foramen ovale. IASD = interatrial septal defect. IVSD = interventricular septal defect. PDA = patent ductus arteriosus. CSF = cerebrospinal fluid. (S) indicates patients who survived.

TABLE II (*contd.*)

No.	Author and year	Sex	Age (years)	Cardiac anomaly	Cyanosis	Digital clubbing	Meningeal reaction	Site of abscess	Organism	Primary focus
25	Ruhberg (1942)	F	6	PS and IVSD	+	+	+	Multiple abscesses in R. occipital lobe	..	Upper respiratory infection at onset of illness
26	Robbins (1945)	F	10	T of F	+	+	+	L. parieto-occipital	Haemolytic streptococci from CSF: haemolytic streptococci, fusiform bacilli, and Borellia vincenti from abscess	..
27	,,	F	19	T of F, but pulmonary atresia; PDA	+	+	+	R. parieto-occipital	Streptococcus from CSF	Gingivitis
28	,,	F	20	T of F; PDA	+	+	+	L. temporal	..	..
29	Currens, Kinney, and White (1945)	M	11	PS; PFO	+	..	..	L. temporo-occipital	..	..
(S)30	Smolik, Blattner, and Heys (1946)	F	9	Uncertain	..	..	..	L. frontal	Haemophilus influenzae	Feverish chill 2 weeks previously
31	Sidenberg, Kessler, and Wolpaw (1946)	M	6	T of F	+	+	+	L. parietal	Staph. aureus, Ps. pyocyanea, and Bact. coli	..
32	Gates, Rogers, and Edwards (1947)	M	6	Cor biatriatum triloculare	..	..	..	L. temporo-occipital	..	Onset 7 days after tonsillectomy
33	,,	M	8	T of F	+	+	..	R. fronto-parietal	Gram-negative anaerobic bacillus	..
34	,,	M	5	T of F	+	+	+	L. fronto-parietal	..	..
35	,,	F	26	IASD	..	..	+	R. parieto-occipital	Actinomyces bovis	Severe upper respiratory infection at onset; acute duodenal ulcer
36	Hand (1947)	M	5	PS; IVSD	+	+	..	3 abscesses in L. cerebral hemisphere: temporal, occipital, and parietal	Gram-positive diplococci	Purulent coryza at onset
37	,,	F	8	Functional cor biloculare; dextrocardia	..	..	+	2 abscesses in R. cerebral hemisphere: occipital and temporal	..	..
(S)38	Brunnschweiler and Streiff (1947–8)	M	13	PS; probable T of F	..	..	..	R. frontal	..	..
39	Parker (1948)	M	26	PS and PFO	+	+	..	R. frontal	Anaerobic diphtheroids	..
(S)40	Oliver and Leese (1949)	M	7	Probable T of F	..	..	+	R. frontal	Aerobic actinomyces	..
41	Blalock and Kieffer (1950)	F	9	PS and PFO	+	..	..	L. frontal	..	..
42	Iniguez, Barrios, di Bello, and Azambuja (1950)	F	36	Probable T of F; dextrocardia	+	+	+	L. frontal	..	..
43	Sancetta and Zimmerman (1950)	F	35	IVSD and PDA	..	..	+	R. temporal	Staph. albus	..

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A Blalock–Taussig anastomosis had been done in Cases 40, 54, 70, 76, and 79. Case 78 was the only one in which the abscess followed pulmonary valvulotomy.

TABLE II (*contd.*)

No.	Author and year	Sex	Age (years)	Cardiac anomaly	Cyanosis	Digital clubbing	Meningeal reaction	Site of abscess	Organism	Primary focus
44	Maronde (1950)	M	26	T of F	..	..	..	R. temporal	..	..
45	,,	F	6	T of F	..	..	..	L. frontal	..	Following appendicitis and peritonitis
46	,,	F	28	IVSD (2)	..	..	..	L. occipital	..	..
47	,,	F	30	IVSD	..	..	..	R. temporal	..	..
48	,,	M	16	IASD and IVSD	..	..	..	R. occipital	..	..
49	,,	F	56	IVSD	..	..	..	R. temporo-parieto-occipital	..	..
50	,,	M	6	IASD; IVSD; rudimentary R. ventricle; small pulmonary artery	..	..	..	1 abscess in each frontal lobe	..	..
51	,,	M	13	IASD and IVSD	..	..	..	2 abscesses in R. cerebral hemisphere: parietal and occipital	..	..
52	,,	F	6	T of F	..	..	..	L. frontal, and smaller abscesses in both parietal lobes	..	..
(S) 53	Sweeney and Patton (1950)	M	10	Probable Eisenmenger complex	+	+	+	L. parietal	..	..
(S) 54	,,	M	8	Probable T of F	+	+	+	R. parieto-occipital	..	Sore throat at onset
(S) 55	Cohen, Bergman, and Malis (1951)	F	22	Probable T of F; PDA	+	..	..	R. temporo-occipital	..	Ill after dental treatment: bacterial endocarditis 2 years previously
(S) 56	Beller (1951)	M	6	Probable T of F	+	+	..	L. parietal	Haemolytic streptococci	..
57	Berthrong and Sabiston (1951)	..	10	T of F	..	..	+	Multiple abscesses in L. temporal and frontal lobes and pons	Actinomyces	..
58	,,	..	5	T of F	..	..	..	L. parietal	..	..
59	,,	..	6	T of F	..	..	..	R. frontal	..	..
60	,,	..	22	IVSD	..	..	..	R. occipital	..	Liver abscess and osteomyelitis of leg
61	Barger, Henderson, and Edwards (1951)	M	30	Ebstein's malformation; IASD	+	..	+	Upper brain-stem	..	..
62	,,	M	6	T of F	..	..	..	Multiple abscesses in L. cerebral hemisphere	Bacteroides organism; anaerobic streptococcus	..
63	Roger, Poursines, and Roger (1952)	M	18	T of F	+	..	+	L. temporal	..	..
	ager and tz (1952)	M	5	Transposition of great vessels; IVSD	+	+	..	L. fronto-parietal (multilocular)	..	..
65	,,	F	4	T of F	+	..	..	R. occipital, extending forwards	Actinomyces	..
66	Gluck, Hall, and Stevenson (1952)	M	7	Transposition of great vessels; PS; IASD; and IVSD	+	+	+	L. temporal	..	..
67	,,	M	12	T of F	+	+	+	L. occipital	..	..

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A Blalock–Taussig anastomosis had been done in Cases 40, 54, 70, 76, and 79. Case 78 was the only one in which the abscess followed pulmonary valvulotomy.

TABLE II (*contd.*)

No.	Author and year	Sex	Age (years)	Cardiac anomaly	Cyanosis	Digital clubbing	Meningeal reaction	Site of abscess	Organism	Primary focus
(S) 68	Ehni and Crain (1952)	F	32	Lutembacher's syndrome; probable IASD	+	+	+	1. R. temporal; 2. L. temporal (interval of 6 years)	1. Actinomyces; 2. Haemolytic streptococci, Staph. aureus, and Haemophilus influenzae	..
69	Genesi (1953)	F	16	T of F	+	+	..	L. cerebellar hemisphere	Staphylococci and actinomyces	..
(S) 70	Avol and Heifetz (1954)	M	11	Probable T of F	..	..	..	L. temporal	Haemophilus influenzae and Staph. aureus	..
(S) 71	Neill (1955)	M	13	Probable IVSD	..	..	+	R. parietal	Anaerobic streptococcus	Chronic upper respiratory infection
(S) 72	,,	M	27	Probable T of F	+	+	+	L. parietal	Haemophilus influenzae	..
73	Present series	F	14	T of F	..	..	+	L. temporo-parietal	..	Upper respiratory infection
74	,,	M	16	T of F	+	+	+	Brain-stem	..	Bronchitis
(S) 75	,,	F	17	Uncertain	+	..	+	L. parietal	Gram-positive cocci	..
76	,,	M	7	PS; IVSD; functionally univentricular	+	+	+	R. frontal	Streptococci and Gram-negative bacilli	..
77	,,	M	36	T of F	+	+	+	L. parietal	Gram-positive cocci and Gram-negative bacilli	..
(S) 78	,,	M	5	Probable T of F	+	+	+	L. frontal	Streptococcus viridans	Bronchitis and dental caries
(S) 79	,,	F	15	Probable T of F	+	+	..	R. parietal	..	Dental caries

T of F = tetralogy of Fallot. PS = pulmonary stenosis. PFO = patent foramen ovale. IASD = interatrial septal defect. IVSD = interventricular septal defect. PDA = patent ductus arteriosus. CSF = cerebrospinal fluid. (S) indicates patients who survived.

A Blalock–Taussig anastomosis had been done in Cases 40, 54, 70, 76, and 79. Case 78 was the only one in which the abscess followed pulmonary valvulotomy.

in 209 autopsies of cardiac malformation in which there was a septal defect (5·2 per cent.). Berthrong and Sabiston (1951) reported five cases of haematogenous brain abscess in 162 autopsies of congenital heart disease, from which patients under one month old and those with very complicated malformations had been excluded (3·1 per cent.). In comparison with these figures, 314 cases of haematogenous brain abscess were found in 75,274 autopsies for deaths from all causes by Gates, Kernohan, and Craig (1950), an incidence of 0·4 per cent. It may be concluded, therefore, that the autopsy incidence of haematogenous brain abscess in congenital heart disease is significantly greater than the autopsy incidence of haematogenous brain abscess in the general population.

Review of Reported Cases

Seventy-two adequately reported cases of haematogenous brain abscess associated with congenital heart disease have been collected, and these, together with the seven cases described in this article, make a group of 79 for analysis (Table II). None of the reported patients had overt bacterial endocarditis, and the case in Group 2(*a*) in the Birmingham series (Table I) has not been included

in Table II for this reason, and because its clinical course and pathological features did not resemble those of the type of case described in the present article.

Sex and age incidence. The sex incidence was approximately equal. Of the 75 patients shown in Table II whose sex could be ascertained, 40 were male and 35 were female. Their average age was 16·3 years. The youngest affected was

TABLE III

Incidence of Haematogenous Brain Abscess in Congenital Heart Disease for each Five-Year Age-Group

Five-year age-group	*Number of cases*	*Five-year age-group*	*Number of cases*
Under 5	2	35 to 39	4
5 to 9	23	40 to 44	0
10 to 14	18	45 to 49	0
15 to 19	14	50 to 54	0
20 to 24	5	55 to 59	2
25 to 29	6		—
30 to 34	5	Total	79

three and the oldest 57 years old. The highest incidence was in the five- to nine-year age-group, but the incidence under the age of five years was remarkably low, only two cases having been reported. Table III shows the number of cases in each five-year age-group. The decline in numbers after the second age-group is due to reduction in the number of patients at risk by deaths from heart failure and other causes.

The cardiac malformation. The various cardiac abnormalities found are listed in Table IV. Sixty-seven cases (84·8 per cent.) showed evidence of a central venous-arterial shunt. Such a shunt may be defined as a mechanism whereby part of the mixed venous blood reaching the heart from the systemic circulation is directed into the aorta without first passing through the lungs. The shunt may be from right to left through a septal defect, or directly into the aorta, as in transposition of the great vessels, dextroposition of the aorta, or a univentricular heart. Of the cases without evidence of a central venous-arterial shunt, one was that reported by Smolik, Blattner, and Heys (1946) in Group D, and the remaining 11 were cases with septal defects included in Group B (Table IV). In the presence of a simple septal defect a left-to-right shunt would be expected because of the higher pressures in the left cardiac chambers, but it is likely that reversal of this shunt may occur intermittently where the defect is relatively large, or terminally as a result of congestive failure. Patency of the ductus arteriosus was recorded in only five of the 62 cases which came to autopsy.

The brain abscess was solitary in 70 (88·6 per cent.) of the 79 cases, and was often well encapsulated when encountered at operation or autopsy. A solitary abscess occurred in the brain-stem in two cases, and in the cerebellum in another two cases. The site of the remaining 66 solitary abscesses occurring in the cerebral hemispheres is indicated in Table V. The cerebral hemispheres were almost equally affected and, allowing for the relatively large size of the frontal

lobes, the abscesses were fairly evenly distributed in the hemispheres. Some were deeply situated in the brain from their commencement. The usual mode

TABLE IV

The Cardiac Malformation in 79 Cases

A. *48 fatal cases: presence of venous-arterial shunt confirmed by nature of cardiac malformation found at autopsy*

Fallot's tetralogy	23	Pulmonary stenosis and interventricular septal defect	5
Resembling Fallot's tetralogy, but pulmonary atresia instead of stenosis	2	Pulmonary stenosis and patent foramen ovale	4
Eisenmenger complex	1	Ebstein's malformation and patent foramen ovale	2
Aorta from right ventricle, pulmonary atresia, and interventricular septal defect	1	Functionally univentricular	4
Transposition of great vessels and interventricular septal defect	5	Cor biloculare	1

B. *14 fatal cases: septal defect found at autopsy, but venous-arterial shunt not anatomically proved*

Interventricular septal defect	8	Interventricular and interatrial septal defects combined	3
Interatrial septal defect, including patent foramen ovale	3		

C. *3 fatal cases: clinical evidence of venous-arterial shunt, but no autopsy*

Probable Fallot's tetralogy	3

D. *14 patients who recovered: clinical evidence of venous-arterial shunt in majority*

Probable Fallot's tetralogy	9	Probable interatrial septal defect	1
Probable Eisenmenger complex	1	Uncertain	2
Probable interventricular septal defect	1		

TABLE V

Site of the Abscess in the 66 Cases of Solitary Abscess in a Cerebral Hemisphere

Site	*Right hemisphere*	*Left hemisphere*	*Total*
Frontal lobe	7	8	15
Parietal lobe	3	7	10
Frontoparietal	4	3	7
Temporal lobe	6	5	11
Temporoparietal	0	2	2
Temporoparieto-occipital	1	0	1
Temporo-occipital	1	2	3
Parieto-occipital	3	1	4
Occipital lobe	5	3	8
Thalamus	0	1	1
Not stated	4	0	4
Total	34	32	66

of termination was by rupture into one of the lateral ventricles, but some caused death by compression of the brain.

Bacteriology. Positive cultures of the contents of the brain abscess were obtained in 22 of the 79 cases (Table VI), but the culture was made during life in only 10 cases. A mixed growth occurred in six cases, but in only two of these

(Nos. 68 and 70 in Table II) was the culture made during life. In Cases 4 and 5 described in the present paper there is little doubt, from examination of stained smears, that two different organisms were present, namely Gram-positive cocci (streptococci in Case 4) and Gram-negative bacilli. These mixed infections are suggestive of an embolic origin, as it is difficult to conceive of reinfection of an established abscess by a new organism from the blood-stream.

Source of infection. There was no clinical evidence of bacterial endocarditis in the 14 patients who survived the abscess, but the patient of Cohen, Bergman, and Malis (1951) had had subacute bacterial endocarditis two years previously.

TABLE VI

Organisms found in 22 Cases in which Cultures were Positive

Organism	*Number of positive cultures*		
	During life	*Post mortem*	*Total*
Haemolytic streptococcus	2	2	4
Streptococcus viridans	2	0	2
Anaerobic streptococcus	1	1	2
Staphylococcus aureus	2	1	3
Staphylococcus albus	0	1	1
Staphylococcus (unspecified)	0	1	1
Diplococcus lanceolatus	0	1	1
Actinomyces	2	2	4
Haemophilus influenzae	4	1	5
Bact. coli	0	2	2
Ps. pyocyanea	0	1	1
Vincent's organisms	0	1	1
Bacteroides	0	1	1
Anaerobic diphtheroids	0	1	1
Total	13	16	29

Positive cultures during life were obtained in Cases 21, 30, 40, 56, 65, 68, 70, 71, 72, and 78 (Table II).

Of the patients who died, three were not examined *post mortem* but had no clinical evidence of bacterial endocarditis, and of the 62 who came to autopsy 57 showed no sign of bacterial endocarditis or endarteritis; in the remaining five cases (Numbers 6, 12, 31, 36, and 76 in Table II) endocardial or endarterial vegetations were found at autopsy. Among the 73 patients (92·4 per cent.) in whom bacterial endocarditis or endarteritis can be excluded with reasonable certainty, only 18 showed evidence of a primary infection. An upper respiratory infection preceded the illness in six cases, and bronchitis in three. Three patients had dental sepsis, and in one of these the illness followed dental treatment. Gingivitis was present in one case, one began with a sore throat, one was preceded by a feverish chill, and another followed tonsillectomy. One case occurred after appendicitis, one after a hand infection, and one in association with osteomyelitis of a limb bone and a liver abscess. In the remaining cases it is probable that infecting organisms entered the body through a relatively trivial breach of its protective epithelium, and excited little inflammatory response either at the portal of entry or on their way to the brain.

Aetiology and Pathogenesis

Because of their frequent association it may be concluded that a central venous-arterial shunt predisposes to the development of a haematogenous brain abscess, the risk of which is probably directly proportional to the volume of the shunt. Reports of haematogenous brain abscess in association with pulmonary angiomata indicate that a pulmonary venous-arterial shunt may be a similar predisposing factor (Wodehouse, 1948; Stern and Naffziger, 1953). By contrast, arteriovenous shunts due to uncomplicated patent ductus arteriosus, extrapulmonary angiomata, or arteriovenous aneurysms of the greater circulation, show no special association with brain abscess. The manner in which the central venous-arterial shunt acts as an aetiological factor has not yet been satisfactorily explained. Paradoxical embolism by a detached fragment of infected peripheral venous thrombus, as suggested by Abbott, Lewis, and Beattie (1923), does not explain the marked predilection for localization of the abscess in the brain, or the lack of concomitant embolic phenomena elsewhere in the body. If it is assumed that these abscesses occur as a result of transient bacteriaemia arising usually in the course of a minor infection, their development in the brain is more easily understood. Transient bacteriaemia seems the most likely explanation for solitary haematogenous brain abscesses occurring in persons who have no cardiac anomaly and no obvious primary infection. There were seven such cases in Group 4(*b*) in the Birmingham series (Table I). It appears that, perhaps because of its vascular architecture, the brain is a particularly susceptible site for abscess formation during the course of a transient mild bacteriaemia. Small bacterial emboli may form spontaneously in the blood-stream in bacteriaemic states, owing to the action of agglutinins or other physico-chemical factors, and an abscess may follow impaction of such an embolus in a capillary or arteriole of the brain. In the presence of a central venous-arterial shunt it is probable that the natural process of clearance of bacteria from the blood-stream is ineffective. One reason for this is that part of the venous return by-passes the pulmonary capillaries, where, according to the experimental observations of Wright (1927) and previous workers quoted by him, a considerable proportion of blood-borne bacteria are filtered out of circulation. Should an ordinarily innocuous bacteriaemia be prolonged in these cyanotic patients, the liability to brain abscess would be correspondingly increased. A special susceptibility of the brain to infection in morbus caeruleus has been suggested (Maronde, 1950; Cohen, Bergman, and Malis, 1951). This susceptibility may be associated with the known tendency towards arterial and venous cerebral thrombosis (Taussig, 1947; Berthrong and Sabiston, 1951), the result mainly of increased blood viscosity caused by polycythaemia. The thrombotic tendency and subnormal oxygen tension in the brain would both favour infarction as a result of septic embolism, and the infarcted tissue, lacking resistance, would enable the infective process to become established. Several authors (Rabinowitz, Weinstein, and Marcus, 1931–2; Wechsler and Kaplan, 1940; Hanna, 1941; Robbins, 1945) considered the possibility of haematogenous infection of a pre-existing cerebral

infarct, but there is little clinical or pathological support for this theory. Furthermore, it is difficult to show from clinical and post-mortem studies that infarction is an essential pathogenetic process in the majority of cases. On the available evidence it is likely that defective elimination of bacteria from the blood-stream is the most important factor in pathogenesis. Further speculation is precluded by the paucity of bacteriological data in these infections, and by our scanty knowledge of changes in structure and function of the brain in morbus caeruleus.

Effect of corrective circulatory operations. Three cases in the present series occurred after corrective circulatory operations—pulmonary valvulotomy in Case 6, and the Blalock–Taussig anastomosis in Cases 4 and 7. The latter operation also preceded the abscess in three other cases shown in Table II. In these six patients the abscess developed at an interval ranging from three months to five years after operation. Death resulted in another case only three days after pulmonary valvulotomy (Blalock and Kieffer, 1950), but the abscess must have been present before operation. Campbell and Deuchar (1953) mentioned the occurrence of a (presumably haematogenous) cerebral abscess three months to three years after operation in five out of 165 patients who had morbus caeruleus and survived a Blalock–Taussig anastomosis. Only one of the 165 patients developed signs of bacterial endocarditis, and the diagnosis was not established for certain in this case. Neither cerebral abscess nor bacterial endocarditis occurred, during a one- to four-year follow-up period, in 50 patients with Fallot's tetralogy who survived pulmonary valvulotomy, infundibular resection, or both (Campbell, Deuchar, and Brock, 1954). Taussig and Bauersfeld (1953) reported 22 cases of bacterial endocarditis in 1,000 cases of operation for pulmonary stenosis and atresia, but did not state the incidence of brain abscess in this group. It is probable that reduction of the total volume of the venous-arterial shunt diminishes proportionately the liability to haematogenous brain abscess. There is no doubt, however, that the special risk of this complication is still present as long as the shunt remains.

Diagnosis

The most important point in diagnosis is awareness of the association between morbus caeruleus and brain abscess, and of the fact that there is often no obvious primary infection. Intense and prolonged headache is by far the commonest initial symptom, but occasionally, as in Case 7 in the present series, focal neurological signs may precede the onset of headache by several days. Fever is seldom a marked feature, but a moderate polymorphonuclear leucocytosis is usually present. Of the 68 patients shown in Table II of whom clinical details are available, 37 (54·4 per cent.) had signs of meningeal irritation, and 24 (35·3 per cent.) had epileptic attacks, which were focal in 13 (19·1 per cent.). When meningeal irritation occurred early, it was presumably due to spread of the initial inflammatory reaction to the ventricle or subarachnoid space. The cerebrospinal fluid in patients who had early meningeal symptoms often showed

a marked cellular response, but seldom contained demonstrable bacteria. In the terminal stage meningitis was due to leakage or frank rupture of the abscess into the ventricular system.

The important conditions to be differentiated are (1) simple cerebral infarction, thrombotic or embolic; (2) subacute bacterial endocarditis with cerebral embolism; and (3) tuberculous or pyogenic meningitis. Simple infarction may be indistinguishable at the onset of the illness in occasional cases in which paralysis precedes the development of headache. The acuteness of the illness will serve to distinguish it from the usually insidious onset of subacute bacterial endocarditis or tuberculous meningitis, but both these maladies may sometimes begin with acute cerebral symptoms. Lumbar puncture has almost invariably been resorted to as a diagnostic procedure, but carries the risk of causing serious brain herniation at the tentorial hiatus or foramen magnum if an abscess is present, and also of precipitating rupture of an abscess into the ventricular system. Localization by clinical means, assisted by the electroencephalographic record, may be sufficiently precise to permit of diagnostic exploration through a burr-hole. Failing this, the key to diagnosis is early pneumoventriculography through burr-holes. This operation appears to do little harm in a case of uncomplicated meningitis or cerebral infarction. Once infection has become localized in the brain, the latent interval of clinical improvement which frequently occurs is apt to lead the clinician to believe that an early suspicion of brain abscess has been erroneous. This interval may be prolonged for several months if antibiotic therapy has been used, as shown by Case 4 in the present series, and by instances in which the patient was well enough to be sent home during the quiescent period (Nos. 42 and 53 in Table II).

Treatment

Recovery from the abscess occurred in three cases in the present series, and in 11 of the previously reported cases shown in Table II. In addition, Campbell and Deuchar (1953) mentioned recovery in four of their five cases. If diagnosis is made early, treatment is likely to be successful, because the abscess is usually solitary. The principles of treatment are the same as for brain abscesses in general, and consist of a combination of appropriate antibiotic therapy and surgery. Early and repeated aspiration of the abscess through a conveniently placed burr-hole is recommended, together with injection of the antibiotic into the abscess cavity and its systemic administration. This conservative method of treatment is the least disturbing to the patient, and can be expected in most cases to sterilize the abscess and reduce it eventually to an innocuous scar. Excision of the encapsulated abscess may occasionally become necessary if the infecting organisms are resistant to antibiotics, or if the capsule is too thick to contract and obliterate the abscess cavity. Broager and Hertz (1952) advocated early radical excision, even before capsule formation has occurred, but this drastic procedure seems to be unnecessary.

I am indebted to the physicians and surgeons who have allowed me to report their cases, to the pathologists who have granted me access to autopsy records, and particularly to Professor E. Brodie Hughes and Dr. Clifford Parsons for criticism of the manuscript.

Summary

Seven cases of solitary haematogenous brain abscess in association with cyanotic congenital heart disease are described. No primary focus of infection was demonstrated for certain in any of these cases, but three patients had had acute respiratory infections. In two cases the abscess developed after a Blalock–Taussig operation, and in one case after pulmonary valvulotomy. Recovery occurred in three cases after antibiotic therapy and aspiration of the abscess, without excision of its capsule. The first six cases represent 8·7 per cent. of 69 cases of haematogenous brain abscess of all types admitted to the United Birmingham Hospitals during the decade 1944 to 1953.

Seventy-two previously reported cases of haematogenous brain abscess in congenital heart disease have been collected, and the whole group of 79 cases is reviewed. The abscesses were solitary in the brain in 70 (88·6 per cent.) of the 79 cases, and had no special site of predilection in the brain. Bacterial endocarditis could be excluded in all but a small minority of cases, and in 55 (69·6 per cent.) of the 79 patients there was no evidence of a primary infection. A central venous-arterial shunt resulted from the cardiac malformation in 67 (84·8 per cent.) of the 79 cases, and may have existed in the remainder.

Haematogenous brain abscess is a common complication of cyanotic congenital heart disease, but the reason for this association remains obscure.

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FIG. 1. Case 3. Anteroposterior radiograph, showing left parietal abscess outlined by thorotrast, and displacement of air-containing right lateral and third ventricles

FIG. 2. Case 3. Lateral radiograph corresponding to Fig. 1

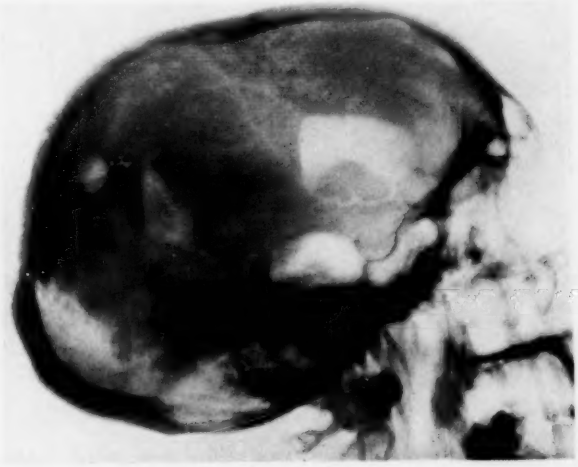

FIG. 3. Case 5. The parietal abscess has ruptured into the ventricular system, which contains air and thorotrast

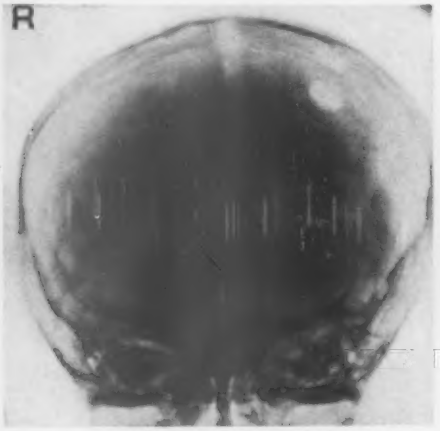

FIG. 4. Case 6. Anteroposterior radiograph, showing thorotrast in left frontal abscess, and gross ventricular displacement

FIG. 5. Case 6. Lateral radiograph corresponding to Fig. 4

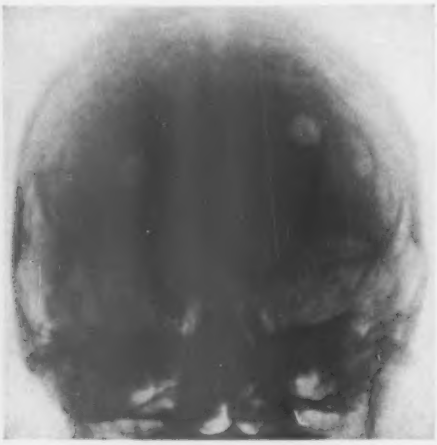

FIG. 6. Case 7. Anteroposterior radiograph, showing abscess outlined by thorotrast

FIG. 7. Case 7. Lateral radiograph corresponding to Fig. 6, showing that the abscess is bilocular. The posterior loculus is probably the older one

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A FIVE-YEAR ASSESSMENT OF PATIENTS IN A CONTROLLED TRIAL OF STREPTOMYCIN, PARA-AMINOSALICYLIC ACID, AND STREPTOMYCIN PLUS PARA-AMINOSALICYLIC ACID, IN PULMONARY TUBERCULOSIS[1]

Report to the Tuberculosis Chemotherapy Trials Committee of the Medical Research Council

BY WALLACE FOX AND IAN SUTHERLAND

(From the Tuberculosis and Statistical Research Units of the Medical Research Council)

IN 1948 a joint sub-committee of the Streptomycin in Tuberculosis Trials Committee of the Medical Research Council and the Research Committee of the British Tuberculosis Association planned a controlled clinical trial of streptomycin and of *p*-aminosalicylic acid (PAS) in the treatment of pulmonary tuberculosis. Patients with acute extensive disease were allocated at random to three series: the patients in one series received streptomycin 1 gm. daily for three months; those in a second series received PAS (sodium salt) 20 gm. daily for three months, and those in the third series received a combination of streptomycin 1 gm. daily with PAS (sodium salt) 20 gm. daily for three months. Detailed results after six months' observation have already been published (Medical Research Council, 1950). Although PAS alone had some therapeutic activity in acute disease, it was inferior both to streptomycin alone and to the combination streptomycin plus PAS. There was a much lower incidence of streptomycin resistance with streptomycin plus PAS than with streptomycin alone. The present report gives the results of a follow-up of the three series of patients for a period of five years after admission to the trial. It represents a parallel study to the five-year follow-up of the first controlled trial of streptomycin in pulmonary tuberculosis (Fox, Sutherland, and Daniels, 1954), in which the effects of streptomycin plus rest in bed were compared with those of rest in bed alone.

I. *Plan and Conduct of the Trial*

The type of case included in the trial was carefully defined as follows: acute, progressive, bilateral pulmonary tuberculosis of presumably recent origin, bacteriologically proved, and unsuitable for collapse therapy; age-group 15 to 30 years. A central panel of clinicians reviewed all cases before acceptance to ensure that they conformed to this definition. Each patient was admitted to one of 10 co-operating centres, and treatment was then decided by reference to a

[1] Received October 22, 1955.

list based upon random sampling numbers, held confidentially in the Council's Tuberculosis Research Unit. This list determined whether the patient received streptomycin alone, PAS alone, or the combination of the two drugs. Of 166 patients studied in the trial, 54 were allocated to the streptomycin (S) series, 59 to the PAS (P) series, and 53 to the streptomycin plus PAS (SP) series.

Treatment and observation. All the patients were admitted to the trial between December 1948 and October 1949. After a week of preliminary investigation and assessment of clinical condition, each patient entered the trial for a period of six months, and the treatment allocated was prescribed for the first three months. Patients in the S series received streptomycin 1 gm. daily in one intramuscular injection; those in the P series received PAS (sodium salt) 20 gm. daily by mouth in four equal doses; those in the SP series received streptomycin plus PAS in doses as for the other two series. All the patients remained in bed in hospital for at least the six-month period, and during this time regular clinical, bacteriological, and radiographic observations were made. From three months onwards the clinician was free to undertake any treatment he wished for patients in any series.

Two-year and five-year assessment. After the six-month assessment the subsequent progress of the patients was studied in the third year after entry to the trial, and again when five years had elapsed since admission. Assessments of clinical condition at the end of two and five years were obtained, together with details of the treatment which each patient had received during the five-year period. Whenever possible a complete series of radiographs was assembled, and those taken on admission to the trial, at three months, at two years, and at five years, were assessed by an independent panel of two radiologists and a chest physician. Bacteriological analyses were impracticable, since many of the surviving patients, both at two and at five years, no longer had active disease, and examinations for tubercle bacilli had been performed very infrequently.

II. *Comparability of the Three Treatment Series*

Interpretation of long-term comparisons. It was shown in the earlier report (Medical Research Council, 1950) that, after random allocation, the distribution of patients according to clinical condition on admission was similar in the three series, except that the SP series had rather fewer very severe cases than the other two. Thus during the first three months, when the series differed only in their chemotherapy, it was legitimate to relate the differences in progress observed to the differences in chemotherapy. After three months the clinician was free to institute whatever treatment he felt would then most benefit the patient. In interpreting long-term results it is thus essential to know what additional chemotherapy and collapse therapy were given to each patient during the five-year period, and whether there were any notable differences between the series in these respects.

Additional chemotherapy during the five-year period. Details of the additional chemotherapy given during the five-year period are set out in Table I. Of the

53 S patients surviving at three months, 43 per cent. received additional chemotherapy during the five-year period, compared with 71 per cent. of 58 P and 54 per cent. of 52 SP patients, the average duration of chemotherapy for those who received it being 6·2, 6·4, and 6·5 months respectively. These averages included between 4·5 and 4·9 months of combined chemotherapy for each series during the period. The timing of the additional chemotherapy has been studied in more detail, since there is evidence that the early administration of chemotherapy for acute bilateral disease in young adults may have an important effect

TABLE I

Additional Chemotherapy during the Five-Year Period

		Period 3 months–5 years						*Patients receiving any form of chemotherapy at some time during the period*					
		Patients receiving any form of chemotherapy			*Patients receiving combined chemotherapy*			*3 months–1 year*		*1–2 years*		*2–5 years*	
Treatment allocated for the first 3 months	*Total patients alive at 3 months*	*No.*	*%*	*Average duration (months)*	*No.*	*%*	*Average duration (months)*	*No.*	*% of survivors at 3 months*	*No.*	*% of survivors at 1 year*	*No.*	*% of survivors at 2 years*
Streptomycin (S) .	53	23	*43*	6·2	19	*36*	4·7	5	*9*	10	*22*	17	*43*
PAS (P) . .	58	41	*71*	6·4	34	*59*	4·5	25	*43*	18	*34*	22	*48*
Streptomycin plus PAS (SP) . .	52	28	*54*	6·5	27	*52*	4·9	15	*29*	15	*30*	16	*33*

on the outcome of the disease (Fox, Sutherland, and Daniels, 1954). During the first year the S series was relatively less favoured than either the P or the SP series in the numbers receiving additional chemotherapy, for 9 per cent. of surviving S patients received courses of chemotherapy after the first three months, compared with 43 per cent. of the P patients and 29 per cent. of the SP patients. In the second year the S patients still remained at a disadvantage, for 22 per cent. received chemotherapy, compared with 34 per cent. of the P and 30 per cent. of the SP patients. Between two and five years the S series was no longer at a disadvantage. The same pattern was found both for courses of a single drug and for courses of combined chemotherapy; the details are not tabulated. In the first year combined chemotherapy invariably consisted of daily streptomycin with a daily dosage of PAS of the order of 20 gm. (sodium salt). During the second year the same combination was used, with a few minor variations. After two years combined chemotherapy often consisted of isoniazid with streptomycin or with PAS.

In sum, comparatively few patients in the S series (25 per cent.) received additional chemotherapy during the first two years. On the other hand the P series received a great deal of additional chemotherapy in the same period, 57 per cent. of the patients having additional courses, mainly consisting of combined chemotherapy. Indeed, they represent a group of patients in whom an initial course of PAS alone was often supplemented subsequently with streptomycin plus PAS. Of the SP patients 44 per cent. had additional chemotherapy during the first two years, mainly consisting of further courses of streptomycin plus PAS, and this series was also more favoured than the S series. *These differences must be borne in mind when assessing the findings for the five-year period.*

TABLE II

Patients with Collapse Therapy or Resection during the Five-year Period

Treatment allocated for the first 3 months	Period 3 months–5 years			Patients with collapse therapy or resection at some time during the period					
				3 months–1 year		1–2 years		2–5 years	
	Total patients alive at 3 months	Patients with collapse therapy or resection							
		No.	%	No.	% of survivors at 3 months	No.	% of survivors at 1 year	No.	% of survivors at 2 years
Streptomycin (S)	53	33	62	25	47	26	57	27	68
PAS (P)	58	47	81	34	59	35	66	37	80
Streptomycin plus PAS (SP)	52	36	69	30	58	34	68	35	73

TABLE III

The Types of Collapse Measure and Resection during the Five-year Period

Treatment allocated for the first 3 months	Total patients with collapse measures or resection	Total procedures	Procedure							
				Artificial pneumothorax					Resection	
			Pneumoperitoneum	Unilateral	Bilateral	Thoracoplasty	Plombage	Extrapleural pneumothorax	Whole lung	Lobe or segment
Streptomycin (S)	33	46	17	7	4	8	1	2*	5	2
PAS (P)	47	68	28	12	8	10*	4	0	3	3
Streptomycin plus PAS (SP)	36	48	16	12	7	8	1*	1	3	0

* Including one bilateral procedure.

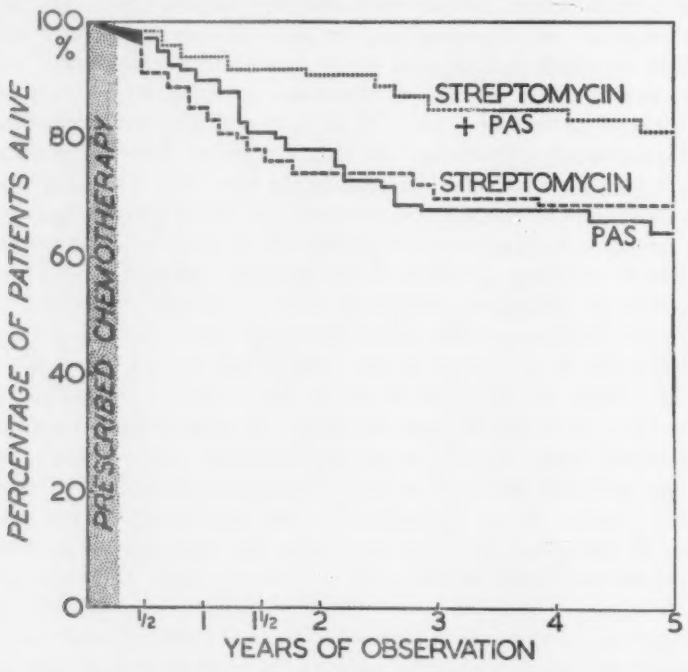
Collapse therapy and resection during the five-year period. The pattern of collapse therapy and resection for the three series is complex, and only the salient features are given. To simplify the presentation a number of conventions have been adopted. A reversible form of collapse therapy has been regarded as established, and included in the tables, only if it was maintained for a period of at least three months. It is certain that in some patients a phrenic-nerve crush or re-crush has not been recorded, and these measures have been excluded. Since a resection and a thoracoplasty are often associated, it was decided that when both measures were applied to the same lung the treatment would be recorded as a resection, whichever operation was performed first, and irrespective of the interval between them. Table II sets out the number of patients who had collapse therapy or resection. The data are presented first for the whole five years and then for three intervals, namely the first year, the second year, and the last three years. Of 53 S survivors at three months, 62 per cent. had some form of intervention in the five years, compared with 81 per cent. of 58 P and 69 per cent. of 52 SP patients. In each sub-period there were rather fewer S patients who had collapse therapy or resection than P or SP patients. Table III classifies the types of collapse measure and the resections. There were 46 procedures in 33 S patients, 68 in 47 P patients, and 48 in 36 SP patients. In all three series reversible collapse measures were frequent. There were 17 pneumoperitoneums in the S, 28 in the P, and 16 in the SP series. Artificial pneumothorax was also a common procedure, and it is of particular interest that a bilateral pneumothorax was used in 19 patients, namely in four of the S, eight of the P, and seven of the SP patients. In one P patient only were the two procedures not simultaneous. Thoracoplasty and plombage were used less frequently in all three series. There were seven resections in the S, six in the P, and three in the SP series. It may be concluded that collapse therapy, both reversible and permanent, was used frequently in all three series, and especially so in the P series.

Reversible collapse therapy at five years and chemotherapy in the fifth year. At the end of five years a number of patients in each series still had an artificial pneumothorax, either unilateral or bilateral, or a pneumoperitoneum. Of the 37 S survivors nine had reversible procedures, as did 11 of 38 P and 13 of 43 SP survivors. A further indication of the amount of active therapy still required towards the end of the five-year period is the number of patients who received chemotherapy in the fifth year. Four of the S, eight of the P, and eight of the SP survivors had some chemotherapy in this year.

III. *Results during the Five-Year Period*

Mortality in the five-year period. The mortality in the five-year period is analysed in Table IV and the Figure. All the deaths were due to pulmonary tuberculosis, except that of one S patient who died of a subarachnoid haemorrhage secondary to malignant hypertension after 46 months. The cause of death was confirmed by a post-mortem examination, which also revealed no evidence of active tuberculosis. Of the deaths due to pulmonary tuberculosis one, in a P patient, was due to an air embolism during a refill of an artificial pneumothorax

after 20 months, and one, also in a P patient, occurred at 26 months, four days after a thoracoplasty with plombage. By the end of five years 31 per cent. of the 54 S, 36 per cent. of the 59 P, and 19 per cent. of the 53 SP patients had died. The substantial advantage to the SP series, although not statistically significant at the end of the period, was apparent throughout the five years. The general pattern of mortality during the period was similar for the S and P series, but



Percentage survival in the three treatment series for a five-year period (53 SP, 54 S, and 59 P patients).

it should be noted that most of the deaths in the S series occurred in the first two years, when 14 patients died, compared with only three in the last three years. For the P series the death rate continued steadily for three years, for six patients died in the first year, seven in the second, and six in the third; thereafter only two patients died. Although the mortality was lower than in the S or P series, most of the deaths in the SP series also occurred in the earlier part of the period. There were eight deaths in the first three years, and only two in the last two years. For all three series combined, 43 of the 166 patients (26 per cent.) were dead by three years, whereas in the last two years of observation only five more patients died, or 4 per cent. of the 123 survivors at three years.

Clinical assessment at two years. The disease in the survivors at two years was classified by the clinician in charge as 'quiescent' or 'active'; the working capacity was recorded as 'full activity', 'modified activity', or 'nil' (for defini-

tions see Appendix). The first part of Table V shows the mortality and disease status of patients in the three series at two years. Of the 54 S patients 35 per cent. had attained quiescence, compared with 36 per cent. of the 59 P and 49 per cent. of the 53 SP patients. The majority of the survivors (second part of Table V) were still classified as having no working capacity, namely 63 per cent. of the S, 76 per cent. of the P, and 65 per cent. of the SP survivors. The three series had fared similarly, except that rather more of the SP patients had quiescent disease, and a rather higher proportion of survivors in the P series had no working capacity.

Radiographic changes in the first two years. Radiographic changes in the first two years were assessed by a panel of three members, Dr. L. G. Blair, Dr. A. F. Foster-Carter, and Dr. G. Simon. In making their assessments the members were unaware to which treatment series each patient had been allocated. Four degrees of improvement were recognized—slight, moderate, considerable, and exceptional; and three of deterioration—slight, moderate, and considerable. In evaluating the changes in the first two years three radiographs were used, namely those taken on entry to the trial, at three months, and at two years. Intermediate films were studied if they were available and were requested. The panel assessments were undertaken and collated in the manner already described (Fox, Sutherland, and Daniels, 1954). No comparisons were possible for the first two years for four S, two P, and two SP patients; relevant radiographs for three patients had been destroyed, and for two had been mislaid; for the other three no radiograph was available within two months of the anniversary. All these eight patients had active disease at two years, and six (two S, two P, and two SP) died in the third year. Of the two remaining S patients one had active and the other arrested disease at five years. The available results are presented in Table VI. Of 50 S patients, 70 per cent. showed moderate, considerable, or exceptional improvement, compared with 61 per cent. of 57 P and 75 per cent. of 51 SP patients. In terms of considerable and exceptional improvement, however, the SP series fared less well than the other two series, the proportions being 50 per cent. in the S, 42 per cent. in the P, and 35 per cent. in the SP series.

Changes in cavitation in the first two years. Changes in the extent of cavitation were assessed from the single postero-anterior radiographs taken on entry to the trial and at two years. Cavitation had disappeared in 18 (64 per cent.) of the 28 S patients with initial cavitation, in 26 (70 per cent.) of the 37 P patients, and in 23 (61 per cent.) of the 38 SP patients. On the other hand one S and one SP patient, in whom no cavitation was apparent initially, had cavitation at two years. It is an indication of the infectivity of patients at two years that cavitation was then visible on a standard radiograph in 11 (31 per cent.) of the 36 S patients, 11 (25 per cent.) of the 44 P patients, and 16 (35 per cent.) of the 46 SP patients.

Clinical assessment at five years. The disease in patients who survived five years was classified as 'arrested', 'quiescent', or 'active', and their working capacity as 'full activity', 'modified activity', or 'nil' (for definitions see

TABLE IV

Mortality in the Three Treatment Series during the Five-Year Period

Treatment allocated for the first 3 months	Total patients	Deaths in the first: 6 months		1 year		18 months		2 years		2½ years		3 years		3½ years		4 years		4½ years		5 years	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Streptomycin (S)	54	5	9	8	15	12	22	14	26	14	26	16	29	16	29	17*	31	17*	31	17*	31
PAS (P)	59	2	3	6	10	11	19	13	22	16	27	19	32	19	32	19	32	20	34	21	36
Streptomycin plus PAS (SP)	53	1	2	3	6	4	8	5	9	6	11	8	15	8	15	8	15	9	17	10	19

* Including one non-tuberculous death.

TABLE V

Mortality and Disease Status of Patients, and Working Capacity of Survivors, in the Three Treatment Series at Two Years

Treatment allocated for the first 3 months	Total patients	Status of patients: Quiescent disease		Active disease		Dead		Total survivors at two years		Working capacity of survivors: Full activity		Modified activity		Nil	
	No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Streptomycin (S)	54	19	35	21	39	14	26	40	100	8	20	7	18	25	63
PAS (P)	59	21	36	25	42	13	22	46	100	7	15	4	9	35	76
Streptomycin plus PAS (SP)	53	26	49	22	42	5	9	48	100	6	12	11	23	31	65

TABLE VI

Changes in Radiographic Appearances in the Three Treatment Series in the First Two Years

Treatment allocated for the first 3 months	Total patients assessed		Improvement								No change		Deterioration								Death	
			Exceptional		Considerable		Moderate		Slight				Slight		Moderate		Considerable					
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%			No.	%
Streptomycin (S)	50*	100	3	6	22	44	10	20	0	0	0	0	1	2	0	0	0	0			14	28
PAS (P)	57*	100	5	9	19	33	11	19	7	12	1	2	0	0	0	0	1	2			13	23
Streptomycin plus PAS (SP)	51*	100	2	4	16	31	20	39	5	10	0	0	2	4	1	2	0	0			5	10

* For 4 S, 2 P, and 2 SP patients one or the other radiograph was not available.

TABLE VII

Mortality and Disease Status of Patients, and Working Capacity of Survivors, in the Three Treatment Series at Five Years

Treatment allocated for the first 3 months	Total patients assessed		Status of patients								Total survivors at 5 years		Working capacity of survivors					
			Arrested disease		Quiescent disease		Active disease		Dead				Full activity		Modified activity		Nil	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Streptomycin (S)	53*	100	11	21	17	32	8	15	17†	32	37	100	24	65	9	24	4	11
PAS (P)	59	100	13	22	19	32	6	10	21	36	38	100	28	74	4	11	6	16
Streptomycin plus PAS (SP)	53	100	13	25	24	45	6	11	10	19	43	100	30	70	7	16	6	14

* For one more patient no assessment of disease status was possible at five years.
† Including one non-tuberculous death.

TABLE VIII

Changes in Radiographic Appearances in the Three Treatment Series in the Five-Year Period

Treatment allocated for the first 3 months	Total patients assessed		Improvement								No change		Deterioration								Death	
			Exceptional		Considerable		Moderate		Slight				Slight		Moderate		Considerable					
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%			No.	%
Streptomycin (S)	53*	100	2	4	25	47	8	15	0	0	0	0	0	0	1	2	0	0			17†	32
PAS (P)	59	100	3	5	25	42	8	14	0	0	0	0	0	0	2	3	0	0			21	36
Streptomycin plus PAS (SP)	53	100	1	2	29	55	12	23	0	0	0	0	0	0	0	0	1	2			10	19

* For one more patient the radiograph on admission was not available.
† Including one non-tuberculous death.

TABLE IX

Changes in Cavitation on Standard Radiographs in the Three Treatment Series in the Five-Year Period

Treatment allocated for the first 3 months	Total survivors at 5 years	Survivors without initial cavitation		Survivors with initial cavitation							
		No change	Appearance of cavitation	Total		Disappearance of cavitation		Cavities smaller or fewer		No change		Cavities larger or more numerous	
				No.	%	No.	%	No.	%	No.	%	No.	%
Streptomycin (S)	37	6	2	29	100	24*	83	4	14	0	0	1	3
PAS (P)	38	6	0	32	100	27	84	3	9	0	0	2	6
Streptomycin plus PAS (SP)	43	7	1	35	100	31	89	3	9	0	0	1	3

* Including one patient for whom the radiograph on admission was not available, and for whom the record of initial cavitation made by an independent assessor for the earlier report (Medical Research Council, 1950) was used.

Appendix). These assessments are given in Table VII. The disease was arrested or quiescent in 53 per cent. of the 53 S, in 54 per cent. of the 59 P, and in 70 per cent. of the 53 SP patients, showing a benefit to the SP series. Although the majority of survivors had returned to some employment, 11 per cent. of S, 16 per cent. of P, and 14 per cent. of SP survivors had no working capacity. In this respect the findings for the three series are similar.

Radiographic changes in the five-year period were evaluated by the panel, using single radiographs taken on entry to the trial, at two years, and at five years, with intermediate films if these were requested. The radiographs were read by the panel members at sessions subsequent to those held for the two-year study. The radiographic information for the five-year period, in contrast to that at two years, is complete except for one S patient for whom the radiograph on admission had been lost. The results for the remaining patients are presented in Table VIII. Of 53 S patients 66 per cent. showed at least moderate improvement, compared with 61 per cent. of the 59 P and 79 per cent. of the 53 SP patients. In terms of exceptional and considerable improvement the SP series held only a slight advantage, the proportions being 51 per cent. for the S, 47 per cent. for the P, and 57 per cent. for the SP series.

Changes in cavitation in the five-year period. Table IX shows the changes in the extent of cavitation during the five-year period for all the survivors. Changes were assessed from the single postero-anterior radiographs taken on entry to the trial and at five years. No tomograms or radiographs taken in special positions were submitted to the panel. Cavitation had disappeared in 83 per cent. of the 29 S survivors who initially had cavitation, in 84 per cent. of 32 P, and in 89 per cent. of 35 SP survivors. Of the patients with no cavitation apparent initially, two in the S and one in the SP series had cavitation at five years. Even after five years seven (19 per cent.) of the 37 surviving S patients, five (13 per cent.) of the 38 P, and five (12 per cent.) of the 43 SP survivors had cavitation visible on a standard radiograph.

Nature of radiographic improvements in the five-year period. The standard radiographs taken on entry to the trial and at the end of five years, for all the patients in whom radiographic improvement had occurred, were submitted to a single independent observer (Dr. G. Simon) for appraisal of the nature of the improvements which had taken place. The study was made without the observer knowing the treatment of any patient, and only major changes were recorded. Improvement was classified under the following headings: resolution, fibrosis, calcification, lobar or segmental atelectasis, reduction in cavitation, and disappearance of cavitation (see Appendix). Resolution was reported in every patient (Table X). Disappearance of, or reduction in, cavitation was a major improvement in 26 of 28 S patients with initial cavitation, in 30 of the 32 P, and in 34 of the 35 SP patients. Calcification occurred in nine S, 13 P, and 12 SP patients. Fibrosis was less frequent, and there were only three instances of atelectasis, one in each series. The major radiographic improvements thus consisted of resolution and disappearance of cavitation, and the nature of the improvements was similar in the three series.

The mortality and course of the disease in the three treatment series have now been described. In the following section a study is made of the extent to which the outcome in each series depended upon the condition of the patients on admission to the trial and upon their response to treatment during the first three months.

TABLE X

Nature of Major Changes in Radiographic Appearances for Patients who showed Radiographic Improvement in the Five-Year Period

		Major radiographic changes							
			Disappearance of cavitation						
Treatment allocated for the first 3 months	*Total patients with radiographic improvement*	*Resolution*	*Without resection*	*Some cavities resected*	*All cavities resected*	*Reduction in cavitation*	*Fibrosis*	*Calcification*	*Lobar or segmental atelectasis*
Streptomycin (S)	35*	35	19	1	3	3	6	9	1
PAS (P)	36	36	23	3	1	3	8	13	1
Streptomycin plus PAS (SP)	42	42	29	1	1	3	7	12	1

* For one more patient no assessment of major changes was possible at five years.

IV. *Prognostic Factors in Acute Bilateral Pulmonary Tuberculosis in Young Adults*

A study has been made of the extent to which the initial clinical condition and the immediate response to treatment affected the prognosis. The mortality during the five-year period, and the disease status of the survivors, have in each series been related to the condition of the patients on admission to the trial, as judged by extent of cavitation, temperature, erythrocyte sedimentation rate (Westergren), and the number of lung zones involved (on a standard radiograph). The mortality and disease status have also been related to sex, and to the response to treatment during the first three months as indicated by changes in the radiographs, erythrocyte sedimentation rate, temperature, and sputum positivity, and the emergence of drug-resistant bacteria.

Cavitation. In the course of the assessments of changes in cavitation during the five-year period, an opportunity was taken to reassess the extent of cavitation on admission to the trial for each patient. An assessment was made for the earlier report (Medical Research Council, 1950), but the reassessment has the advantage of being made by Dr. L. G. Blair, the assessor of extent of cavitation for the five-year follow-up of the first trial of streptomycin (Fox, Sutherland, and Daniels, 1954), which facilitates a comparison of the long-term results in the two trials. The reassessment also incorporates a modification of technique; having made his assessments, the assessor reviewed the radiographs in each cavitation category, as a group, to confirm the homogeneity of the group

TABLE XI

*Mortality and Disease Status at Five Years, according to the Extent of Initial Cavitation**

Treatment allocated for the first 3 months	*Extent of initial cavitation*	*Total patients*	*Death within 5 years*	*Disease status of survivors at 5 years*		
				Active	*Quiescent*	*Arrested*
Streptomycin (S) .	3-plus	8	7	0	0	1
	2-plus	23	5	5	9	4
	1-plus	14	4†	2	4	4‡
	Nil	8§	1	1	4	2
PAS (P) . .	3-plus	13	11	1	0	1
	2-plus	24	7	2	10	5
	1-plus	14	1	3	6	4
	Nil	8	2	0	3	3
Streptomycin plus PAS (SP) . .	3-plus	7	2	1	2	2
	2-plus	27	8	3	12	4
	1-plus	11	0	1	6	4
	Nil	8	0	1	4	3
All treatment series	3-plus	28	20	2	2	4
	2-plus	74	20	10	31	13
	1-plus	39	5	6	16	12
	Nil	24	3	2	11	8

* Recent reassessment. For details see text.
† Including one non-tuberculous death.
‡ Including one patient for whom the radiograph on admission was not available and the earlier assessment of extent of initial cavitation was used.
§ For one more patient no assessment of disease status was possible at five years.

TABLE XII

Mortality and Disease Status at Five Years, according to Temperature on Admission

Treatment allocated for the first 3 months	*Average evening temperature during week of preliminary investigation*	*Total patients*	*Death within 5 years*	*Disease status of survivors at 5 years*		
				Active	*Quiescent*	*Arrested*
Streptomycin (S)	100° F. or more	15	10*	0	4	1
	99°–99·9° F.	18	5	2	9	2
	Under 99° F.	16†	2	3	4	7
	No fever	4	0	3	0	1
PAS (P)	100° F. or more	16	11	1	3	1
	99°–99·9° F.	18	4	2	6	6
	Under 99° F.	20	5	2	8	5
	No fever	5	1	1	2	1
Streptomycin plus PAS (SP)	100° F. or more	14	4	3	5	2
	99°–99·9° F.	19	2	2	7	8
	Under 99° F.	13	1	1	9	2
	No fever	7	3	0	3	1
All treatment series	100° F. or more	45	25	4	12	4
	99°–99·9° F.	55	11	6	22	16
	Under 99° F.	49	8	6	21	14
	No fever	16	4	4	5	3

* Including one non-tuberculous death.
† For one more patient no assessment of disease status was possible at five years.

and to see whether any individual radiograph should be upgraded or downgraded. The new assessments have been used to study mortality and disease status in relation to initial cavitation (Table XI). Combining the figures for all three treatments, 20 (71 per cent.) of 28 patients with 3-plus cavitation on admission were dead within five years, compared with 20 (27 per cent.) of 74 with 2-plus cavitation, five (13 per cent.) of 39 with 1-plus cavitation, and three (12 per cent.) of 24 with no cavitation. Extensive cavitation was, however, a less adverse prognostic sign in the SP series than in the S or P series, five of seven SP patients with 3-plus cavitation surviving for five years, compared with only one of eight similar S, and two of 13 P patients. Little association is apparent between the disease status of the *survivors* at five years and the extent of their initial cavitation.

Temperature. Table XII relates the mortality and disease status in the three series to the average evening temperature during the week of preliminary investigation. In the S and P series the same pattern appears as for cavitation, the most febrile patients having the worst prognosis. Thus 10 of the 15 S and 11 of the 16 P patients with an average evening temperature of 100° F. or more died within five years, compared with seven of 38 S and 10 of 43 P patients who were in the lower categories of pyrexia, or apyrexial. In contrast, the SP patients showed little association between mortality and degree of initial pyrexia.

Other criteria. There was only a slight association between the erythrocyte sedimentation rate and the mortality in each of the three treatment series, and the results have not been tabulated. The association between the number of lung zones involved (recently assessed by an independent observer) and mortality was more marked, for 21 (49 per cent.) of 43 patients with six zones involved had died within five years, compared with 10 (18 per cent.) of 56 patients with involvement of four zones or less. The patterns were similar for the three treatment series taken separately.

Mortality and disease status related to sex. Table XIII sets out the mortality of male and female patients in the three series for the five-year period, and also the disease status of the survivors at five years. This table is of particular interest, since, after six months' observation (Medical Research Council, 1950), female patients had fared better radiographically than male, the differences in results for all female compared with all male patients being at that time statistically significant. At five years, however, the differences between the sexes in mortality and disease status were unimportant, 32 per cent. of 72 men and 27 per cent. of the 93 women having died; 56 per cent. of the men and 61 per cent. of the women had arrested or quiescent disease. It is noteworthy that, as in the earlier report, the female patients in the SP series fared particularly well; only two (7 per cent.) of the 30 patients had died, and 77 per cent. had arrested or quiescent disease.

Mortality and disease status related to early radiographic response. Table XIV presents the mortality during the five-year period, and the disease status of the survivors, in relation to radiographic changes during the first three months, as

TABLE XIII

Mortality and Disease Status at Five Years, according to Sex

Treatment allocated for the first 3 months	*Sex*	*Total patients* No.	%	*Death within 5 years* No.	%	*Disease status of survivors at five years* *Active* No.	%	*Quiescent* No.	%	*Arrested* No.	%
Streptomycin (S)	Male	19*		7		4		6		2	
			100		*37*		*21*		*32*		*11*
	Female	34		10†		4		11		9	
			100		*29*		*12*		*32*		*26*
PAS (P)	Male	30		8		4		13		5	
			100		*27*		*13*		*43*		*17*
	Female	29		13		2		6		8	
			100		*45*		*7*		*21*		*28*
Streptomycin plus PAS (SP)	Male	23		8		1		9		5	
			100		*35*		*4*		*39*		*22*
	Female	30		2		5		15		8	
			100		*7*		*17*		*50*		*27*
All treatment series	Male	72		23		9		28		12	
			100		*32*		*13*		*39*		*17*
	Female	93		25		11		32		25	
			100		*27*		*12*		*34*		*27*

* For one more patient no assessment of disease status was possible at five years.
† Including one non-tuberculous death.

TABLE XIV

*Mortality and Disease Status at Five Years, according to Changes in Radiographic Appearances in the First Three Months**

Treatment allocated for the first 3 months	*Changes in radiographic appearances in first 3 months**	*Total patients alive at 3 months*	*Death within 5 years*	*Disease status of survivors at 5 years* *Active*	*Quiescent*	*Arrested*
Streptomycin (S)	Deterioration or no change	15	12	2	0	1
	1-plus improvement	25†	3	4	12	6
	2-plus or 3-plus improvement	12	1‡	2	5	4
PAS (P)	Deterioration or no change	30	14	2	7	7
	1-plus improvement	23	4	4	10	5
	2-plus or 3-plus improvement	5	2	0	2	1
Streptomycin plus PAS (SP)	Deterioration or no change	12	3	3	6	0
	1-plus improvement	31	5	3	15	8
	2-plus or 3-plus improvement	9	1	0	3	5
All treatment series	Deterioration or no change	57	29	7	13	8
	1-plus improvement	79	12	11	37	19
	2-plus or 3-plus improvement	26	4	2	10	10

* As assessed in the earlier report (Medical Research Council, 1950).
† For one more patient no assessment of disease status was possible at five years.
‡ A non-tuberculous death.

assessed by the original radiological panel (Medical Research Council, 1950). Of 15 S patients who had failed to improve radiographically during this period, 12 (80 per cent.) died within the five years, compared with four (11 per cent.) of 38 who had shown radiographic improvement; in the P series 14 (47 per cent.) of 30 patients who had shown no improvement died, compared with six (21 per cent.) of 28 who had improved; in the SP series three (25 per cent.) of 12 patients without radiographic improvement died, compared with six (15 per cent.) of 40 who had improved. Thus failure to show early radiographic improvement was a bad prognostic sign in the S series, and a relatively unfavourable one in the P series. It was of less prognostic importance in the SP series. Similar findings emerged from an analysis of mortality in relation to the radiographic changes in the first six months.

Mortality and disease status related to early clinical response. No close association was apparent between the early changes in erythrocyte sedimentation rate or in temperature and the outcome at the end of five years; the figures have not been tabulated.

Mortality and disease status related to early bacteriological response. In Table XV the mortality and disease status at five years are related to the bacterial content of the sputum at three months. In this table a single test has been recorded for each patient, namely that nearest to the date of the completion of the prescribed chemotherapy, provided that this was within a week of three months. Of 25 S patients who had had a positive result on direct examination, 12 died within five years, compared with three of 25 patients bacteriologically negative on direct examination. For the P series the corresponding figures were 10 deaths among 24 patients with a positive result on direct examination and six among 26 with a negative result on direct examination. The persistence of a positive sputum on direct examination was thus a relatively unfavourable sign in both the S and P series. In the SP series, on the other hand, there was little association between mortality and the early bacteriological findings.

Mortality and disease status related to the emergence of drug-resistant bacteria. Of the 53 S survivors at three months, four persistently yielded negative cultures after the first month. Of the remaining 49, 39 (80 per cent.) yielded resistant[2] bacilli at some time during the six months. In the upper part of Table XVI the mortality and the disease status of the S series at five years are related to the highest streptomycin resistance ratio obtained during the first six months. Of 20 patients with a resistance ratio of 100 or more, 12 (60 per cent.) had died, compared with three (10 per cent.) of 29 patients with less resistant or sensitive strains. It cannot, however, be concluded with certainty that the emergence of high degrees of resistance influenced unfavourably the subsequent course of the disease, for, as was shown in the earlier report (Medical Research Council, 1950), the patients in whom high degrees of resistance emerged were, as a group, more acutely ill on admission to the trial. It is worthy of note that six patients who had organisms with a resistance ratio of 100 or more had arrested or quiescent disease at five years. A corresponding study of mortality

[2] Taking a resistance ratio of 8×H37Rv as the lower limit of resistance.

and disease status was undertaken for the P series. Unfortunately information on PAS resistance was lacking in 23 patients, and the study is thus incomplete (lower part of Table XVI). Of 13 patients with resistant[3] organisms in the first

TABLE XV

Mortality and Disease Status at Five Years, according to Bacterial Content of the Sputum at Three Months

Treatment allocated for the first 3 months	*Results of single bacteriological examinations at 3 months*		*Total patients with specimens tested*	*Death within 5 years*	*Disease status of survivors at 5 years*		
	Direct examination	*Culture*			*Active*	*Quiescent*	*Arrested*
Streptomycin (S)	Positive	Positive or negative	25	12	6	7	0
	Negative	Positive	14	3	2	4	5
	Negative	Negative	11	0	0	6	5
PAS (P)	Positive	Positive or negative	24	10	3	5	6
	Negative	Positive	11	2	1	4	4
	Negative	Negative	15	4	2	6	3
Streptomycin plus PAS (SP)	Positive	Positive or negative	14	3	2	6	3
	Negative	Positive	9	1	3	4	1
	Negative	Negative	29	5	1	14	9
All treatment series	Positive	Positive or negative	63	25	11	18	9
	Negative	Positive	34	6	6	12	10
	Negative	Negative	55	9	3	26	17

TABLE XVI

Mortality and Disease Status at Five Years, according to Bacterial Resistance during the First Six Months

Treatment allocated for the first 3 months	*Highest resistance ratio during the first 6 months*	*Total patients with information available*	*Death within 5 years*	*Disease status of survivors at 5 years*		
				Active	*Quiescent*	*Arrested*
Streptomycin (S)	*Streptomycin:*					
	1,000 or more	3	2	0	1	0
	100–999	17	10	2	4	1
	8–99	19	3	5	6	5
	Under 8	9*	0	1	5	3
PAS (P)	*PAS:*					
	100–999	8	5	0	1	2
	8–99	5	2	0	2	1
	Under 8	23	6	4	6	7

* For one more patient no assessment of disease activity was possible at five years.

six months, seven (54 per cent.) died within five years, compared with six (26 per cent.) of 23 with sensitive organisms. As in the S series, the patients in

[3] Taking a resistance ratio of 8×H37Rv as the lower limit of resistance.

whom PAS-resistant strains emerged were initially more ill than those with sensitive organisms. Three patients who had organisms with a resistance ratio of 100 or more during the first six months had arrested or quiescent disease at five years. Of the SP patients, eight were found to have resistant[4] organisms during the first six months, six to streptomycin, one to PAS, and one to both drugs. Two of the patients with organisms resistant to streptomycin, and the patient with organisms resistant only to PAS, died within five years. Of the other five, two had arrested and one quiescent disease at five years.

Discussion

This report presents a long-term follow-up of all the 166 patients in the Medical Research Council's second controlled clinical trial of chemotherapy in the treatment of pulmonary tuberculosis. Three treatments were studied, namely, streptomycin alone, PAS alone, and the combination streptomycin plus PAS, the treatments being allocated for a period of three months by a random procedure. All the patients were young adults with acute extensive bilateral disease. A report at the end of six months' observation (Medical Research Council, 1950) showed that streptomycin plus PAS and streptomycin alone were each clearly superior to PAS alone, and that there was a much lower incidence of streptomycin resistance with streptomycin plus PAS than with streptomycin alone. An assessment of the three series of patients has now been made for a period of five years from the start of the trial. The additional chemotherapy and the collapse therapy received by patients in the three series after the first three months have an important bearing on the interpretation of these long-term results. Compared with the other two series, patients in the streptomycin (S) series received little additional chemotherapy in the first two years, and they represent a group whose chemotherapy in the crucial phase of treatment usually consisted of streptomycin alone for three months. In contrast, the PAS (P) series received much additional chemotherapy both in the first and in the second year, usually courses of streptomycin plus PAS; these patients thus represent a group whose early chemotherapy was PAS alone, frequently followed by combined chemotherapy. The streptomycin plus PAS (SP) series also received considerable amounts of additional chemotherapy, usually the same combination. The three series therefore differed widely in the chemotherapy that they received in the five-year period. There were also differences in the collapse measures undertaken, a greater proportion of P patients receiving some form of intervention than patients in the other two series.

By the end of the five-year period 31 per cent. of the 54 S patients had died, and 53 per cent. had quiescent or arrested disease; the corresponding figures for the 59 P patients were 36 per cent. and 54 per cent., and for the 53 SP patients 19 per cent. and 70 per cent. Although the benefit to the SP series at the end of the period does not attain statistical significance, it reflects a consistent trend throughout the five years. The finding that the mortality and disease status of the S and P series are so similar at the end of five years is

[4] See footnote, p. 237.

worthy of comment, since at the end of six months the P series had lagged substantially behind the S series in the important radiographic assessment, the differences at that time attaining statistical significance (Medical Research Council, 1950). It seems probable that the frequent administration of streptomycin plus PAS to patients in the P series, after the termination of the prescribed course of PAS, was able to redress this original disadvantage. The SP series also received more additional chemotherapy during the first two years than the S series, and it is probable that the more favourable findings in the SP series at the end of five years are related to this factor, as well as to the difference in the initial course of chemotherapy.

Quite apart from the considerable mortality, acute bilateral disease in young adults is serious and incapacitating, for many patients had active disease and were incapable of work for long periods. Combining the three series, at two years 68 per cent. of the 134 surviving patients were classified as having no working capacity, and even at five years the proportion was 14 per cent. of the 118 survivors. At five years also, cavitation was visible on a standard radiograph in 14 per cent. of the surviving patients. Thus many patients were presumably still infectious. The amount of active treatment undertaken, even towards the end of the period of follow-up, also indicates the persistently serious nature of the disease. In the fifth year 20 patients received some chemotherapy, and at the end of the five years 33 patients still had reversible collapse measures (artificial pneumothorax or pneumoperitoneum). Moreover, only 4 per cent. of the survivors at the end of three years died in the following two years. It may be concluded that a number of patients in this trial have become stabilized in a state of persistent active disease with cavitation. The medical and social welfare of such persons is a great responsibility to the community. It will be of considerable importance to study the fate of the survivors for a further period of years, to see what course is followed by the disease in patients with residual active lesions.

An analysis was made of some of the clinical features on admission to the trial, to see how these affected the prognosis. Extensive cavitation and a high initial pyrexia were unfavourable prognostic signs in the S and the P series. It is noteworthy, however, that the prognosis in the SP series was less closely related to these initial clinical features. For example, whereas seven of eight S patients with extensive (3-plus) cavitation died, as did 11 of 13 similar P patients, there were only two deaths among seven similar SP patients. Involvement of all six lung zones was a bad prognostic sign in all three series, but a high erythrocyte sedimentation rate was comparatively unimportant. In contrast to the findings at the end of six months (Medical Research Council, 1950), which showed a better response in female than in male patients, there was little difference in mortality and disease activity between the sexes at the end of five years. The outcome was also related to the immediate response to treatment. Failure to improve radiographically in the first three months, and a sputum positive on direct examination at the end of three months, each carried a relatively bad prognosis. Again, these associations were less noticeable in the SP

series than in either of the other two series; for example, 12 of 15 S and 14 of 30 P patients who showed no early radiographic improvement died within five years, compared with three of 12 similar SP patients. In the S series, organisms with high degrees of streptomycin resistance tended to emerge during the first six months in patients who were most ill on admission, and the emergence of such strains was associated with a bad prognosis. In the P series the emergence of PAS resistance was also an unfavourable sign.

This long-term follow-up has shown that the group of patients who initially received streptomycin plus PAS made the most satisfactory progress. The initial effectiveness of this combination, the fact that further courses were often given, and the low incidence of bacterial resistance to each of the drugs, probably all contributed to this result. There is further evidence of the effectiveness of streptomycin plus PAS, for the subsequent use of this combination was able to redress the early disadvantage to the patients treated with PAS alone. It is also of particular interest that the prognosis for patients treated with the drugs in combination was not so closely related to the initial clinical features, or to the immediate response to treatment, as for patients receiving either drug alone.

It is of value to compare the five-year progress of the 54 patients treated originally with streptomycin alone in this trial with that of the group of 55 patients who received similar treatment in the first Medical Research Council trial (Fox, Sutherland, and Daniels, 1954). Daniels and Hill (1952) showed that the distributions of severe and less severe illness among all patients on admission were very similar in the two trials, and this is also true of patients allocated to the S series in each trial. The recent reassessment, by one assessor, of the extent of cavitation on admission, has confirmed the close similarity of the two series in this important feature. Moreover, radiographic progress in the two series during the first six months of observation was very similar (Daniels and Hill, 1952). It is therefore of particular interest that at the end of five years 69 per cent. of the patients in the S series in the second trial had survived, 53 per cent. having quiescent or arrested disease, compared with a survival rate of only 42 per cent. in the first trial, 35 per cent. having quiescent or arrested disease, these differences being statistically significant. Even at the end of two years the survival rate in the S series was 74 per cent. in the second trial, and only 56 per cent. in the first trial. Further investigation has shown that there was more additional chemotherapy, and a higher incidence of major surgical measures (though not of minor collapse therapy), in the first two years for the S patients in the second trial. Thus 13 of the S patients in the second trial received additional chemotherapy with streptomycin plus PAS, or PAS alone, in the first two years, compared with only four of the corresponding patients in the first trial; in the same period major surgery was performed in 12 S patients in the second trial (six had a thoracoplasty, three a resection, two an extrapleural pneumothorax, and one a plombage), and in only two patients (both had a thoracoplasty) in the first trial. In addition to these obvious differences, it seems likely that the management of all cases in the second trial was

superior, as a result of a fuller understanding of the scope and application of chemotherapy and of surgery, in patients who had already received some chemotherapy. Moreover, during the two years which elapsed between the trials, both PAS and resection had been introduced in this country. It is reasonable to conclude that all these influences contributed to the superior results in the more recent S series, and the differences are a striking measure of the advances in treatment that occurred between the trials.

The progress in all three series in the present trial, throughout the five years, is in notable contrast to that of the patients with similar disease in the first trial who were treated initially with rest in bed alone (the control series); at the end of two years 62 per cent. of the control patients were dead, compared with 26 per cent. of the S series, 22 per cent. of the P series, and only 9 per cent. of the SP series in the present trial; at the end of five years the corresponding figures were 67 per cent., against 31, 36, and 19 per cent. The comparatively low mortality in the SP series is gratifying, but still leaves considerable scope for further advance. A five-year follow-up of the patients in the third trial of chemotherapy in acute bilateral pulmonary tuberculosis in young adults (Medical Research Council, 1952) is at present in progress. In this trial three different dosages of PAS, each in combination with streptomycin 1 gm. daily, were studied. When this follow-up is complete, further comparisons of the five-year findings for the different treatment series in all three trials will be reported.

Acknowledgements

The long-term follow-up of the patients in this trial was initiated by the late Dr. Marc Daniels. We are indebted to him for his insistence that chemotherapy in pulmonary tuberculosis should not be judged solely by its short-term effects. We regret that it is not possible to name individually all of the large number of clinicians whose willing co-operation has made this follow-up possible. They provided many clinical data, and loaned the radiographs for independent assessment; we wish to thank them for the completeness of the resulting information. We should like to acknowledge in particular the valuable assistance of Drs. J. R. Bignall and Hector J. T. Ross, who between them provided follow-up information for no less than one-quarter of the patients.

APPENDIX

The following definitions of radiological zones of the lung were used: *Upper zone*: the area above a straight line running through the lower borders of the anterior ends of the second ribs. *Middle zone*: the area bounded by the above line and one running through the lower borders of the anterior ends of the fourth ribs. *Lower zone*: the remainder of the lung below the middle zone.

The definitions of disease activity were taken from the Revision of Section I of the Appendix to the Ministry of Health Memorandum 37/T (Revised), with the one exception that no patient who still had a reversible form of collapse therapy was considered to have 'arrested' disease. The relevant definitions are:

"'*Active cases.*" Those not quiescent. All cases discharging tubercle bacilli within the preceding three months should be considered as "active".

'"*Quiescent.*" Cases in which the general condition and exercise tolerance are good, having regard to the extent of the lesion; which show no evidence of toxaemia; in which no tubercle bacilli have been found on three consecutive monthly examinations by stained film; and in which changes revealed by other clinical investigations and by serial skiagrams point to retrogression of the tuberculous lesion.

'"*Arrested.*" Cases in which the disease has been "quiescent" for a continuous period of at least TWO years.'

The following definitions of working capacity were used: '*Full activity*': patient in full-time employment, or undertaking normal housework. '*Modified activity*': patient in part-time employment, or undertaking limited housework. '*Nil*': patient's activity severely limited, or patient confined to bed.

In the assessment of major radiographic changes the following definitions were adopted: *Resolution*: the disappearance or diminution in size of one or more of the lesions. *Fibrosis*: (*a*) appearance of linear shadows, *or* (*b*) diminution in size of lesions, associated with sharpening of their outline or increase in their density; often associated with evidence of lung shrinkage, such as displacement of the trachea, vessels, or a fissure. *Reduction in cavitation*: cavities smaller or fewer, or both, on postero-anterior radiographs. *Disappearance of cavitation*: disappearance of all cavitation on postero-anterior radiographs.

Summary

All the 166 patients in the Medical Research Council's second controlled clinical trial of chemotherapy in the treatment of pulmonary tuberculosis have now been followed up for five years or until death. The patients, who were young adults with acute, bilateral, and progressive pulmonary tuberculosis of recent origin, were treated in hospital for six months, and were allocated at random to a three-month course of chemotherapy, consisting of streptomycin 1 gm. daily (54 S patients), or *p*-aminosalicyclic acid (PAS), sodium salt, 20 gm. daily (59 P patients), or the combination of the two drugs (53 SP patients). On entry to the trial the distribution of patients with severe and less severe illness was similar in the three series.

The long-term findings in the three series cannot be attributed solely to the initial course of chemotherapy, because there were also differences between them in subsequent chemotherapy and collapse therapy. The P series received the most additional therapy, and the S series the least.

By the end of five years 31 per cent. of the S, 36 per cent. of the P, and 19 per cent. of the SP patients had died; 53 per cent. of the S, 54 per cent. of the P, and 70 per cent. of the SP patients had arrested or quiescent disease. The benefit to the SP series was evident throughout the five years. The radiographic disadvantage to the P series compared with the S series, which had been noted at the end of six months, was apparently redressed by the subsequent difference in additional treatment. Similarly, the continued satisfactory progress of the SP series compared with the S series was probably in part due to the fact that the former received more subsequent treatment.

At the end of two years, in the three treatment series combined, 68 per cent. of the 134 surviving patients had no working capacity, and even after five years

the proportion was 14 per cent. of the 118 survivors. Fourteen per cent. of the survivors at five years had cavitation visible on a standard radiograph. Thus the survivors still present a considerable medical and social problem.

The outcome of the disease in the S and P series was less favourable in patients who had extensive cavitation, extensive involvement of the lung zones, or high pyrexia, on admission to the trial. It was also less favourable in S and P patients who failed to improve radiographically, who remained bacteriologically positive at the end of three months, or who developed organisms resistant to streptomycin or to PAS within the first six months. These associations were less close in the SP series.

A comparison, as regards five-year progress, of the 54 patients initially treated with streptomycin alone in this trial with the 55 like patients treated similarly in the first Medical Research Council trial, shows a considerable benefit to the later series, attributable to more additional chemotherapy and major surgical measures, as well as to a fuller understanding in the second trial of the applications of chemotherapy and surgery.

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616.36-004:616.89-008

THE NEUROPSYCHIATRIC SYNDROME ASSOCIATED WITH HEPATIC CIRRHOSIS AND AN EXTENSIVE PORTAL COLLATERAL CIRCULATION[1]

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With Plates 19 and 20

Maniacal paroxysms complicating acute jaundice were recognized by Hippocrates (460–370 B.C.), who commented, 'Those who are mad on account of phlegm are quiet, but those on account of bile are vociferous, vicious, and do not keep quiet'; and the ominous significance of neuropsychiatric disorder in this condition was appreciated by Galen (A.D. 131–200) and Celsus (*c.* A.D. 30). This belief in the influence of liver function on personality, behaviour, and physical infirmity had its origins in the humoral pathology which dominated medical practice for many centuries. Disease was attributed to derangement of the humours, and the liver, elaborating yellow bile (choler) and black bile (melancholy), was the supposed seat of love and violent passion. The amorous Orsino in *Twelfth Night*, belittling the female capacity for sustained devotion, said, 'Alas, their love may be call'd appetite—no motion of the liver, but the palate.' Modern English usage perpetuates another doctrine of Shakespeare's time: 'How many cowards . . . who inward searched, have livers white as milk.' Scientific progress in the eighteenth and nineteenth centuries was incompatible with retention of the humoral basis of disease, and the status of the liver declined from that of a 'vital organ' to a 'great, dull bile producer'. More recently, however, the relationship between hepatic function and neuropsychiatric disorder has again been emphasized, and the syndrome of 'hepatic coma' has been elaborated to include an immense variety of clinical features. Morgagni (1761) recognized an initial phase in which patients were stupid and forgetful and suffered from a 'suppression of the senses', later followed by violent delirium, progressing to terminal coma. Cheyne (1817) observed perseveration of posture; Bright (1836) described the monotonous, impoverished speech which may precede coma, and also recorded headache, delirium, and constant jactitations in a patient with hepatic cirrhosis. On the other hand, delirium and tremor in patients with cirrhosis were ascribed to alcohol by Copland (1858), and Budd (1845) considered that in cirrhosis 'the intellect and senses were free from disorder till the last'; Frerichs (1860) commented that 'jaundice may cause great exhaustion, sadness, peevishness', and realized that 'in chronic cases they may occur independently, then betokening nervous disorders which

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do not depend on jaundice'. Reviewing 31 fatal cases of 'acute yellow atrophy', he amplified neurological signs recorded earlier, and contributed less common findings. One patient exhibited 'general tremulousness', and another, although drowsy by day, passed restless nights. While conceding that similar disorder might result from any disease which caused 'complete disorganization of the liver', Frerichs noted neurological disturbance, always of a less violent nature, in only three of 36 fatal cases of cirrhosis, and deemed these signs to be 'foreign to the disease'.

The view that a neurological syndrome of the same basic pattern may result from liver disease of varied aetiology has now been accepted, and recent work stresses characteristic abnormalities of consciousness and the motor system as the predominant abnormalities in 'hepatic coma'. This conclusion confirms the significance of muscular rigidity (Jenkins, 1884), reflex changes (Rolleston, 1912), ankle clonus (Willcox, 1919), and other signs recorded earlier. Turner, Snavely, Grossman, Buchanan, and Foster (1944) were impressed by the high incidence of tremor and ankle clonus in 'hepatic coma', while Lucké (1944) stressed the prevalence of increased tendon-reflexes and muscular rigidity. Pyramidal and striatal signs were found to be equally prominent by Stokes and Miller (1947). It remained for Adams and Foley (1953) to give a comprehensive account of the characteristic features of 'hepatic coma'. Confusion, lethargy, and inappropriate behaviour were associated with increased reflexes and rigidity during 'impending coma'. They stressed the diagnostic importance of the characteristic 'flapping' tremor, which was observed in nearly every patient, and described typical changes in the electroencephalogram.

The protean nature of the disturbance and the absence of specific neuropathological findings suggest that 'hepatic coma' is of metabolic origin. Deranged nitrogen metabolism was demonstrated by Phillips, Schwartz, Gabuzda, and Davidson (1952), who induced the characteristic neurological and electroencephalographic changes of 'impending hepatic coma' in a proportion of patients with hepatic cirrhosis by the administration of large amounts of dietary protein, ammonium salts, or urea. Methionine was later shown to have a similar effect (Phear, Ruebner, Sherlock, and Summerskill, 1956). Construction of a portacaval anastomosis in the dog (Eck, 1877) was followed by neurological disorder after protein feeding (Hahn, Massen, Nencki, and Pawlow, 1892), and this phenomenon of 'meat intoxication' was elaborated by Baló and Korpássy (1932). Alterations of consciousness with neurological disorder in the human subject, similar to those witnessed in 'hepatic coma', were reported by McDermott and Adams (1954) as a sequel to portacaval anastomosis with resection of a pancreatic neoplasm. White, Phear, Summerskill, and Sherlock (1955) observed that toxic nitrogenous substances from the portal vein can reach the systemic circulation by passing through a diseased liver or through portal-systemic collateral vessels, and this fact explains how similar neuropsychiatric features may be produced by nitrogenous substances in both hepato-cellular failure and portacaval anastomosis. The patient described by McDermott and Adams exhibited fluctuating disorders of consciousness and the motor system

for several months ('episodic stupor'), thus suggesting the possibility that 'hepatic coma' may also occur in a chronic form. Osler (1892) was aware that cerebral symptoms—either noisy, joyous delirium or stupor, coma, or even convulsions—unrelated to jaundice, alcohol, or acholia, might occur at any stage of cirrhosis. Review of the literature reveals that patients in whom chronic or intermittent neuropsychiatric disorder was associated with hepatic cirrhosis have often presented diagnostic problems. The patient reported by Brouwer (1936) had characteristic features of nitrogen intolerance, and in three of the patients described by Waggoner and Malamud (1941) chronic confusion, tremor, rigidity, and dysarthria were observed. Whitfield and Arnott (1951) reported a similar case. Zillig (1948) studied a number of patients with liver disease who showed psychiatric changes. The unfamiliar association of psychotic tendencies with tremor and ataxia in a patient with cirrhosis prompted Greenfield (1954) to speculate on the wider 'clinico-pathological significance of hepato-lenticular degeneration'. Sherlock, Summerskill, White, and Phear (1954) described five patients in whom chronic dementia, with the neurological features of 'hepatic coma' (portal-systemic encephalopathy), was associated with hepatic cirrhosis. They were able to demonstrate an extensive portal-systemic collateral circulation in each patient, and showed that the neuropsychiatric condition was ameliorated by protein restriction, whereas excess of dietary protein and other nitrogenous substances precipitated deterioration. Nervous disorder often dominates the clinical picture, and the presence of liver disease with an extensive portal-systemic collateral circulation may be relatively difficult to establish, thus exposing such patients to the hazard of being regarded simply as neurological or psychiatric problems. In the present paper the characteristic syndrome and methods of diagnosis are amplified. Special reference is made to associated abnormalities of the portal circulation and their relationship to portal hypertension.

Patients Studied (Table I)

The 10 female and seven male patients were aged between 22 and 68 years. Sixteen patients suffered from portal cirrhosis, which was confirmed by needle liver biopsy in six and at autopsy in seven other patients; in no case was alcoholism an aetiological factor, but four patients gave a history of previous hepatitis. The remaining patient developed biliary cirrhosis after a traumatic stricture of the common bile duct. Neuropsychiatric complications had lasted six months to six years, and were the presenting feature in eight patients in whom liver disease had hitherto remained unsuspected. This had led to the admission of four patients to a mental hospital, and in three other cases a psychiatric opinion had been sought. The causes of death in seven patients were cerebral thrombosis, meningitis, gastrointestinal haemorrhage from ruptured oesophageal varices, progressive hepato-cellular failure (two patients), and a terminal acute portal-vein thrombosis (two patients). Unequivocal evidence of liver disease was not constant. Only three patients were icteric, but seven had hepatomegaly, and ascites had occurred at some time in seven. The diagnosis, however, could

usually be supported by the finding of palmar erythema, 'vascular spiders', finger clubbing, or loss of body hair. Fetor hepaticus was prominent in every patient. Clinical evidence of portal hypertension usually rested on splenic

TABLE I

Patients, Diagnosis, Evidence of Liver Disease, and Duration of Neuropsychiatric Disorder

Patient No.	*Sex*	*Age (years)*	*Diagnosis*	*Jaundice, hepatomegaly, or ascites*	*Duration of neuropsychiatric disorder (years)*	*Comments*
1	M	60	Portal cirrhosis	Transient ascites	3	..
2	F	57	Portal cirrhosis	Hepatomegaly	4	Died. Cerebral thrombosis
3	M	42	Portal cirrhosis	..	2½	Syndrome followed portacaval anastomosis
4	M	51	Portal cirrhosis	..	2	Died. Meningitis
5	F	36	Portal cirrhosis	Ascites		Died. Gastrointestinal haemorrhage
6	M	40	Portal cirrhosis	..	1½	..
7	F	41	Portal cirrhosis	..	5	Died. Liver failure
8	F	52	Portal cirrhosis	..	1	Died. Terminal portal-vein thrombosis
9	F	68	Portal cirrhosis	Hepatomegaly	2	..
10	M	42	Portal cirrhosis	..	¾	Syndrome followed portacaval anastomosis
11	F	63	Portal cirrhosis	..	1	Syndrome followed portacaval anastomosis
12	F	22	Portal cirrhosis	Transient ascites	¾	Syndrome followed portacaval anastomosis
13	M	61	Biliary cirrhosis	Jaundice, hepatomegaly	¾	Stricture of bile duct
14	M	37	Portal cirrhosis	Hepatomegaly, ascites	6	Died. Terminal portal-vein thrombosis
15	F	59	Portal cirrhosis	Jaundice, hepatomegaly, transient ascites	1½	..
16	F	50	Portal cirrhosis	Hepatomegaly, transient ascites	½	
17	F	48	Portal cirrhosis	Jaundice, hepatomegaly, transient ascites	1	Died. Liver failure

enlargement, which was a constant finding. Portal collateral vessels in the abdominal wall were visible in two patients, and a loud venous hum was at one time audible in Patient No. 6, although it disappeared subsequently. Gastrointestinal haemorrhage occurred in two other patients. Patients 1 to 5 have been described previously (Sherlock, Summerskill, White, and Phear, 1954). The diagnosis in Patients 4 and 5 was retrospective, and clinical details have been amplified by reference to case records.

Methods

Routine methods of psychiatric case-taking and examination were amplified by special examination of organic mental functions (Mayer-Gross and Guttmann, 1937). The level of consciousness was graded according to response to stimuli. The neuropsychiatric examination was performed at least once daily. Liver function was assessed clinically and by serial biochemical tests. The extent of the portal-systemic collateral circulation was demonstrated by trans-splenic portal venography (Atkinson, Barnett, Sherlock, and Steiner, 1955) in 12 of the 17 patients. Barium-swallow examination for varices was performed in 16 patients, and autopsy evidence was available in seven patients. The degree of portal hypertension was estimated by measurement of the intrasplenic pressure (Atkinson and Sherlock, 1954) in 11 patients, and by the occluded pressure in the hepatic vein (Paton, Reynolds, and Sherlock, 1953) in five patients. Comparison of blood-ammonium values in the hepatic and peripheral veins (White, Phear, Summerskill, and Sherlock, 1955) was used to confirm the presence of a portal collateral circulation in five patients. Tolerance of nitrogenous substances was estimated under strict clinical and biochemical control by the oral administration of *dl*-methionine (Phear, Ruebner, Sherlock, and Summerskill, 1956), ammonium chloride, or a high-protein diet. Blood-ammonium levels were measured by a minor modification (Phear, Sherlock, and Summerskill, 1955) of the method of Conway (1950). Additional investigations included estimation of the glucose, urea, and electrolyte levels in the blood, examination of the cerebrospinal fluid, and electroencephalographic records.

Neuropsychiatric Changes

The 17 patients presented the psychiatric picture of a chronic organic reaction with acute exacerbations; in addition, functional psychotic and psychoneurotic reactions were released in 12 patients. Variability was a marked feature, and in some cases periods approximating to complete remission occurred. The neurological syndrome was clearly defined, but wide fluctuations were seen which were sometimes, although not invariably, related to similar alterations in the mental condition. Gross neurological disorder often remitted within a day of the initial examination; recurrent relapses followed an identical pattern in the same person, but varied in degree and extent from patient to patient. During periods of relative well-being, objective findings were often limited to a characteristic facies, unobtrusive tremor, and mild exaggeration of tendon-reflexes. Deterioration was accompanied by a progressive disorder of speech, gross tremor, exaggeration of reflexes, muscle rigidity, and ankle clonus. In deep stupor or coma flaccidity, absence of reflexes, and certain additional signs might occur.

Disorders of consciousness. All patients showed disturbance of consciousness, with disorder of sleep. Hypersomnia was an early feature, and progressed to an inversion of the sleep rhythm. Overpowering attacks of sleep by day were found in three patients.

Patient 4 was obliged, while driving his car, to pull into the kerb and sleep.

Later this occurrence was conditioned to the 'Stop' sign of traffic lights, and he had to be roused with a prod at the 'Go'. Patient 12, when sleep could not be safely indulged, experienced a sense of detachment and of being elevated and floating in space, together with a seductive feeling of 'not caring', against which she had to struggle.

Reduction in spontaneous movement, a fixed stare, apathy, and slowness and brevity of response were early signs. Further deterioration resulted in reaction only to intense or noxious stimuli. Coma at first resembled normal sleep, but progressed to complete unresponsiveness, with foetal attitudes, rigidity, and irregular stertorous breathing. Deterioration might be arrested at any level, with either regression or persistence of symptoms. Rapid changes in the level of consciousness were accompanied by delirium. Episodic 'twilight states', with wandering and amnesia, started and stopped abruptly, and might continue for hours.

Patient 3, setting out to market, behaved in a confused fashion, paying twice for purchases and failing to recognize relatives. Recovering suddenly in a busy street, he had no recollection of his previous conduct.

Personality changes. All patients showed varying degrees of remittent personality change, which might precede other symptoms. During acute exacerbations behaviour was often uninhibited. Previous personality trends were intensified in six patients (Nos. 4, 7, 8, 10, 13, and 17).

Patient 14 became irritable, violent, childish, and unreasonable, showing a lack of concern for his family. Patient 6, because of his violence towards his children, advised his wife to lock them up. Patient 1, a Presbyterian minister, flirted with nurses, calling them 'sweetheart'. Patient 17, who was sensitive and retiring, avoided social contacts even with relatives. The personality of Patient 4, previously a jovial extrovert, was caricatured.

All the patients, when these changes remitted, showed many personality features of frontal-lobe involvement. They were co-operative and had social ease, and with varying euphoria went jocularity and a tendency to pleasantry. They were unselfconscious, direct, and occasionally tactless, with little drive or initiative. Although aware of their disability and expressing dread of the recurrence of coma, they were generally cheerful people, not given to worrying, with a ready smile and a philosophical attitude.

Patients 12 and 3, who were both slightly ataxic, on a social outing together 'allowed for a few bumps' while walking, and enjoyed the joke when patient 12, through visual disorder, rested her hand on a bald head in the cinema. Patient 8 feared coma because she might misappropriate other people's belongings. Patient 11 worried because 'I wee when I don't know I'm weeing.'

Affect. Although the mood fluctuated, it usually remained constant for several days or weeks at a time. Seven patients (Nos. 3, 8, 10, 11, 12, 13, and 14) had phases of both depression and euphoria, with abrupt changes. Four patients showed changes of mood in the direction of depression only, and five in the direction of euphoria. Patient 7 was exceptional in her stable mood and objective attitude towards herself, relinquished only at the height of stupor, when rage reactions occurred.

Organic mental functions. Amnesia covered episodes of stupor and coma, and when these were prolonged there were anterograde and retrograde extensions. Only two patients showed spontaneous confabulation, although during stupor it could be induced in others. When patients were accessible their memory for remote events was usually unimpaired, although recent memory, as tested by three-minute retention and digit-span methods, was progressively impaired, paralleling deterioration in other neurological and mental functions.

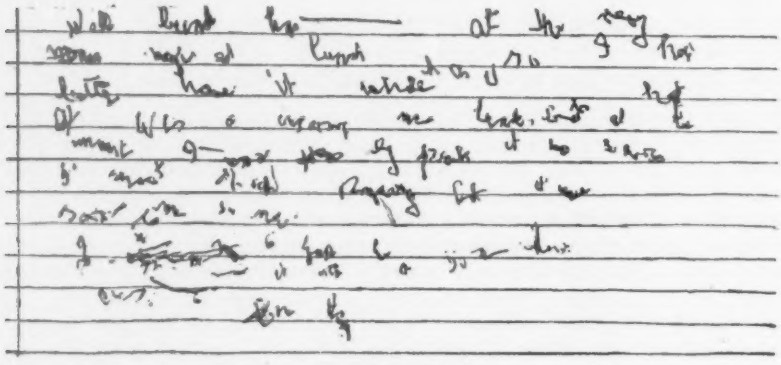
Patient 12, emerging from a three weeks' coma, had no recollection either of the preceding surgical operation of portacaval anastomosis or of her life for several years previously. Letters arrived from apparent strangers, referring to events of which she knew nothing. She inquired what she did for a living. She made a determined effort to 'piece things together', noting down any recovered memories, since she was aware of their evanescence. She concluded that she was in hospital because of a head injury with loss of memory. The abdominal scar was denied, and the news in the daily papers regarded as a fairy tale. Three months later retrograde amnesia had shrunk to a few days, but brief periods of amnesia still occurred daily. Remarks she had made were not remembered the following day and, until insight was full, she accused her relatives of telling lies about her.

The level of attention fluctuated with changes in consciousness, but in stupor perseveration affecting posture, movement, and speech, produced apparent indistractibility.

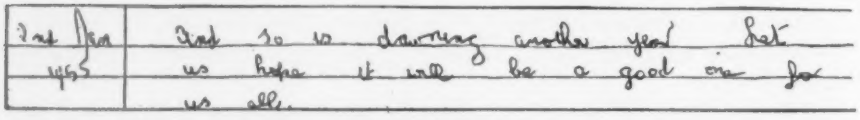
Knowledge of time was disturbed before that of place or of identity of self and others. Momentary disorientation in space was found on waking, and intervals of time appeared longer. Capacity to orientate in space was disturbed at an early stage of stupor. The patient would get lost in his own home, be unable to find doors and light-switches, and have difficulties in dressing. Patient 9, although able to make a well-known bus journey correctly, did so with two stockings on one leg and a hair-net over her hat. Difficulty in subtracting preceded other arithmetical difficulties, and might persist when consciousness was clear and neurological signs minimal or absent. Visual agnosia was shown in seven patients with clouded consciousness. During their nocturnal wanderings they would urinate into various containers such as drawers, baths, or shoes. Patient 3, although seeing clearly, would shave with his toothbrush and clean his teeth with hair cream. Confronted with his breakfast tray, he had to stop and think 'That is the marmalade and that is the sugar basin.'

Articulatory disturbances were proportional to the degree of ataxia and incoordination. Speech was slow and slurred, the voice monotonous and often faint. In deep stupor dysphasia became marked, and was always combined with perseveration. Patient 7, attempting precise articulation, achieved a slow staccato speech. Tongue biting and protrusion occurred during eating and speaking in two patients (Nos. 3 and 7), and the same patients complained of episodic inability to speak. In Patient 3 fine tremors of the lips and nasolabial folds, and tic-like movements of the tongue, accompanied attempted speech. Patient 9 retained emotional speech, while propositional speech was lost. She responded to auditory and painful stimuli by perseverating 'oh, dear', and later with baby

talk, 'do, do, do' and 'ba, ba, ba'. Complicated rhythms were preserved throughout stupor, but pitch was lost. Patient 15, wakened from stupor and asked where she was, replied 'This is Hammer' (yawns) 'This is young son,



December 29, 1954



January 2, 1955

FIG. 1. The writing of Patient No. 7. December 29, 1954: 'Well lunch has at the very moment lunch has . . . so I had better have it while it is hot.' The rest is difficult to decipher. January 2, 1955: the writing is legible.

no, young or younger, young up, uncopac, m—m. Well, well, well, m—m, well, m—m' (smiles). 'Young up, bill, pepel, m—m, m—m, pepel, m, wavent pement wave, pe'man't wave', and so on. The next day speech was normal.

Loss of visual acuity, incoordination, and tremor contributed to writing difficulties. Omission of single letters, reversal of order, and mis-spellings were common in the early phases. With deterioration the writing became more tremulous, letters were superimposed, and lines of writing converged. When still able to attempt writing, the patient became unable to sign his name or to move the pen from left to right. The handwriting was a good index of progress (Fig. 1). In remission Patient 14 had an isolated agraphia for cursive writing, and Patient 12 slight spelling difficulties. Constructional apraxia occurred early, and often persisted when consciousness was clear and neurological signs minimal. Progressive difficulty in copying simple designs in matches accompanied deterioration, but, if tremor, incoordination, and visual disorder were gross, the results of these tests were unreliable. Intermittent difficulty in constructing a five-pointed star in matches was found in patients whose symptoms had otherwise remitted. The earliest complaint of Patient 9 was inability to make the complex designs of Fair-Isle knitting.

Eight patients experienced paraesthesiae in the absence of objective sensory

disturbance. Three had pain in the trunk or extremities, and in one patient the pain led to unsuccessful local surgical intervention. Three complained of hot and cold feelings. Sixteen patients complained of headache, usually fronto-temporal or occipital. All patients intermittently suffered from blurred or double vision. Visual fields were full when co-operation allowed perimetry. In four patients there was lateral or slow rotatory nystagmus. In deep coma dilated pupils, with slow pendulum nystagmus, were constant, and in stupor there was sometimes spasmodic upward deviation of the eyes. Two patients experienced illusionary movement of visual objects, with macropsia and distortion. Unformed visual hallucinations (flashing lights, stars) were found in 10 patients, and in five were coloured, usually red and green. Complex visual hallucinations occurred in five patients, of whom three saw deceased relatives.

Patient 14, in the early stages, saw 'red and only red', and had a compulsion to stare at red objects. Patient 7 complained of intermittent loss of vision, of 'bobbing about' of visual objects, and of seeing bright stars, red and green. Flowers appeared 'unpleasant'. She continued to see her visitors when she knew they had gone. She laughed at her brother's head, which seemed enormous and distorted. During a prolonged stupor hallucinations were 'relentless', of detailed panoramic scenes in bright colours, of frightening bears and wolves, and of names, including catchwords such as 'Esso' and 'Kensitas'. She also had synaesthesia. A dripping tap in her right peripheral field of vision was experienced as a cold drip on her right cheek, sounds of approaching feet as 'people walking over my brain', and her name written as if it had just been spoken.

Three patients had simple auditory hallucinations, and one heard repetition of the words 'dead lost', in keeping with her depressed mood. Hallucinations were tactile in two patients, and olfactory and gustatory in two others. Patient 8, subject to paraesthesiae, complained of mice in her bed. Patient 16 had rectal and facial paraesthesiae, and smelling ether she believed she was being anaesthetized. Loss of awareness of body position was associated with clouding of consciousness, and contributed to the difficulty in dressing. Two patients (Nos. 4 and 12) showed loss of kinaesthetic body-image. Insight was good during remission. Catastrophic reactions in patients failing in arithmetical tests were less common than rationalization of the disability. With deterioration, euphoric patients became amused at their difficulties, and in stupor insight was lost.

Functional reactions. Eight patients (Nos. 3, 5, 8, 11, 12, 13, 16, and 17) had depressive episodes of varying duration and intensity. Two (Patients 8 and 16) of this group, and two others (Patients 7 and 14), showed abortive paranoid states. Two (Patients 4 and 10) had hypomanic reactions, and one (Patient 12) suffered anxiety attacks when she emerged from coma. Two patients (Nos. 3 and 14) showed compulsive behaviour, and also had tics, in one facial, in the other respiratory. The type of functional reaction could be related to the previous personality. Depressive episodes were usually short and mild, and occurred at any stage of the illness. The hypomanic reaction was short-lived in one patient, but persistent in the other.

Patient 12, receiving a higher protein diet than usual, was depressed, with

no interest, not wanting to talk or read. She felt herself a nuisance and preferred to be alone, but denied worrying about her illness. She told her boy friend not to visit, as she became irritable. She was tired and languid, content to sit and do nothing. Patient 16, aged 50, previously a stable personality, had depressive episodes two years, and again four months, before neurological changes developed. They were both related to environmental stress. She wrote to her sister 'It does not seem worth while going on.' A therapeutic high-protein diet precipitated neurological symptoms with temporary euphoria. When the neurological signs lessened she was again depressed, and talked of suicide. In Patient 4 hypomania lasted two years, and he was sent to many psychiatrists. He was noisy, truculent, and argumentative in the ward. During convalescence he enjoyed being driven around Brighton as a prospective purchaser of new, large, and expensive cars, which he could not possibly afford.

Paranoid symptoms, based on perceptual difficulties and misinterpretations, were common during stupor, and more prolonged paranoid reactions were also encountered.

Patient 8, after recovering from a stupor, said 'I thought there was a conspiracy against me, and that the day-nurse told the night-nurse not to speak to me.' She spoke so consistently about her maltreatment that the medical staff were persuaded to consider it as a possibility. Patient 16 developed systematized delusions of persecution by the staff and other patients. She believed that the contents of the daily paper and wireless programmes referred to her. Recovery followed withdrawal of dietary protein.

Disorder of the motor system. The disturbance of motor function showed pyramidal and extrapyramidal elements. The characteristic 'flapping' tremor was best demonstrated in outstretched arms, as a series of irregular, intermittent flexion-extension movements, absent during rest and greatest on sustained posture (for example, placing the finger on the nose). It was usually bilateral, although not bilaterally synchronous. Intentional movement was disrupted in the more severely affected patients, preventing manual tasks and rendering the gait ataxic. Articles were liable to be dropped from the hands. Tremor was aggravated by physical fatigue, anxiety, or excitement. It was invariably present at some stage, and constituted the major neurological disability in nine patients. During remission it disappeared or lost its 'flapping' quality, but it became progressively more prominent during relapses, again becoming difficult to elicit when consciousness was dimmed. Deep tendon-reflexes were exaggerated, increasing with deterioration. Patients during deep coma became flaccid and lost their reflexes. Increased muscle-tone was present at some stage in 12 patients, always with advanced neuropsychiatric disorder. Rigidity usually persisted throughout passive flexion and extension. 'Clasp-knife' or 'cog-wheel' rigidity was sometimes observed. These signs were always most prominent in the lower limbs. Bilateral inequality of muscle-tone and reflexes was often noted. Sustained ankle clonus was associated with rigidity in eight patients. The plantar reflexes were usually flexor, although unilateral or bilateral extensor plantar reflexes, in the absence of gross deterioration, were elicited in four patients, and in all but two patients when observed in deep stupor or coma. The unusual combination of muscle rigidity, ankle clonus, and

flexor plantar responses was therefore frequent. Less common abnormalities of the motor system during relapses were loss of associated movement in nine patients, muscle weakness, and perseveration of posture. Signs during periods

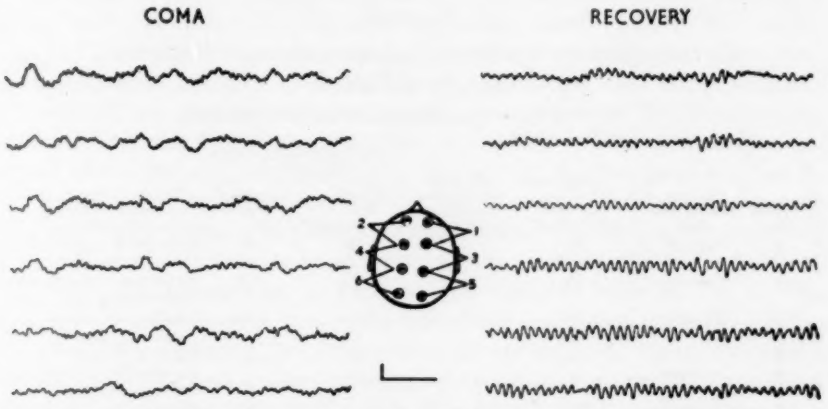


FIG. 2. The electroencephalogram of Patient No. 2 during, and seven days after, an episode of coma.

of deterioration included bizarre choreo-athetoid movements (Patient 7), catatonia (four patients) and muscle twitchings and jerkings (three patients).

Additional neurological findings. An expressionless facies and vacant stare were constant. In eight patients the features were distorted by periodic blinking, yawning, or fatuous grimacing; head-nodding or chewing movements occurred in five patients during relapses. Nine patients had excessive salivation, and the remainder admitted to this symptom on direct questioning.

Electroencephalogram. Observations were made on 16 patients, and all showed abnormalities. Deterioration was associated with slowing of the dominant rhythms from the alpha to the theta and delta ranges. Fast beta activity was seen, sometimes associated with alpha rhythms. Bursts of generalized slow rhythms were encountered, and random slow waves were sometimes present in the fronto-temporal areas. Remission was associated with return of the electroencephalogram to normal (Fig. 2).

Portal Circulation

Splenomegaly was constant. Varices were demonstrated by barium-swallow and barium-meal examination in only five of 16 patients, and examination of the faeces for occult blood was usually negative. The finding of a normal occluded hepatic-vein pressure with an elevated intrasplenic pressure supported the diagnosis of portal-vein occlusion in two patients (Nos. 1 and 2), and in Patient 2 later autopsy showed the portal vein to have been recanalized. Both occluded hepatic-vein and intrasplenic pressures were normal in two patients (Nos. 3 and 8), one of whom had a patent portacaval anastomosis. The presence

of a collateral circulation was suggested by the blood-ammonium level in the peripheral veins exceeding the level in the hepatic vein in five patients (Nos. 1, 2, 3, 7, and 8). Normal intrasplenic pressures were found in three patients

TABLE II

Investigation of the Portal-Systemic Collateral Circulation and Portal Pressure

(V) = percutaneous trans-splenic portal venography.
(A) = autopsy.

Patient No.	*Barium swallow and meal*	*Intrasplenic pressure (mm. Hg) (normal < 17)*	*Occluded hepatic-vein pressure (mm. Hg) (normal < 13)*	*Blood ammonium-nitrogen levels (mg./ml.)*		*Extent of portal-systemic venous collateral circulation*
				Hepatic vein (normal < 1·0)	*Peripheral vein*	
1	Varices	25	7	1·20	1·55	Extensive; portal-vein thrombosis (V)
2	Varices	20	10	0·77	1·41	Extensive; portal-vein thrombosis (V and A)
3	Negative	18	10	0·99	2·46	Patent portacaval anastomosis (V)
4	..	..	..	..	..	Extensive (A)
5	Varices	..	..	..	..	Extensive; portal-vein thrombosis (A)
6	Negative	11	..	..	2·26	Extensive; patent umbilical vein (V)
7	Negative	23·6	6	1·69	2·67	Extensive; patent umbilical vein (V and A)
8	Negative	6	8	1·12	2·03	Extensive; portal-vein thrombosis and large inferior mesenteric vein (V and A)
9	Negative	14	..	..	2·50	Extensive; portal-vein thrombosis and large inferior mesenteric vein (V)
10	Negative	12	..	..	2·90	Portacaval anastomosis (V)
11	Negative	11	..	..	2·10	Portacaval anastomosis (V)
12	Negative	..	..	..	2·00	Portacaval anastomosis (V)
13	Negative	..	..	..	2·95	? (Venography contra-indicated)
14	Varices	24·5	..	..	1·61	Extensive (V). Terminal portal-vein thrombosis (A)
15	Negative	..	..	..	1·71	? (Venography contra-indicated)
16	Varices	12	..	..	2·53	Extensive (V)
17	Negative	..	..	..	..	Extensive (A)

after successful portacaval anastomosis, and in four others who had spontaneously developed widespread anastomotic channels.

The portal venous collateral circulation was further evaluated by percutaneous trans-splenic portal venography in 12 patients, and by post-mortem examination in seven patients, four of whom had previously been investigated by portal venography. Thrombotic occlusion of the portal vein was demonstrated in five patients. In three (Nos. 1, 2, and 5) the portal blood was diverted to the systemic system through multiple anastomotic vessels. This condition is illustrated in Patient 1 (Plate 19, Fig. 3). The splenic vein is outlined, and so is a very short section of the portal vein, which beyond this point appears to be

occluded. The blood seems to have been diverted through the left gastric and para-oesophageal collateral vessels, as well as the inferior mesenteric and some parasplenic veins. In the other two patients (Nos. 8 and 9) the larger portion of portal blood entered greatly distended inferior mesenteric veins, and hence passed to the systemic veins. This condition is illustrated in Patient 8 (Plate 19, Fig. 4). The splenic vein is clearly outlined and of considerable calibre, and appears to drain directly into the inferior mesenteric vein. The portal vein was not outlined, nor were any collateral vessels. It is of interest that there was no evidence of portal hypertension in these two patients (Table II), despite the extent of the portal-systemic collateral circulation. In four patients (Nos. 3, 10, 11, and 12) neuropsychiatric disorder had followed a few days to one year after the construction of a portacaval anastomosis. Investigations suggested that the shunt was patent, and portal venography confirmed this fact in Patients 3 and 10. The appearances in Patient 3 are shown in Plate 19, Fig. 5. The splenic vein and a short section of the portal vein, as well as the inferior cava, are clearly demonstrated. No collateral vessels are outlined. The calibre of the splenic and portal vein is normal. In two patients (Nos. 6 and 7) the umbilical vein was grossly dilated. A loud venous hum, with a thrill, was once present in Patient 6, but latterly the thrill disappeared, and the hum became soft and inconstant. Patient 7 did not have an abdominal venous hum. Trans-splenic venography revealed the nature of this anastomosis, which could not be demonstrated by other methods. In Patient 7 (Plate 20, Fig. 6) the contrast medium outlined the portal and splenic veins clearly, and filled the small, distorted, intrahepatic branches of the portal vein. A very large umbilical vein was seen to fill from the left branch of the portal vein, diverting the bulk of the contrast medium through inferior epigastric and iliac veins into the inferior vena cava. No other collateral vessels were seen. This anatomical relationship was confirmed by dissection at autopsy (Plate 20, Fig. 7). Similar appearances, with the additional filling of the left gastric and para-oesophageal veins, were seen in Patient 6. In four patients (Nos. 4, 14, 16, and 17) a patent portal vein was associated with an extensive collateral circulation through multiple smaller vessels. The venogram of Patient 16 (Plate 20, Fig. 8) is typical of the appearances in this group. The splenic vein is filled, and so is the portal vein. A very extensive collateral circulation is demonstrated through the left gastric and para-oesophageal veins, and also through some lumbar veins, the left suprarenal vein, and inferior vena cava. The intrahepatic branches of the portal vein are grossly distorted. In two patients (Nos. 13 and 15) the presence and nature of the collateral circulation remains uncertain, as portal venography was precluded by a bleeding tendency secondary to liver disease.

Liver Function

Liver-function tests (Table III) usually, but not always, supported the diagnosis of cirrhosis. The serum-bilirubin level was raised in half of the patients, but values over 2 mg. per 100 ml. were frequent in only two patients. In nine patients the serum-albumin level was below 3 gm. per 100 ml., and in six the

TABLE III

Liver Function Tests and Routine Biochemistry

N.V. = normal values

Patient No.	*Serum-bilirubin (mg./100 ml.)*	*Serum-albumin (gm./100 ml.)*	*Serum-globulin (gm./100 ml.)*	*Thymol turbidity (units)*	*Zinc sulphate turbidity (units)*	*Colloidal gold turbidity (units)*	*Serum alkaline phosphatase (King-Armstrong units)*	*Serum-cholesterol (mg./100 ml.)*	*Bromsulphthalein retention (% at 30 minutes)*	*Prothrombin time (seconds)*	*Serum-sodium (mEq./litre)*	*Serum-potassium (mEq./litre)*	*Serum-chloride (mEq./litre)*	*Serum-bicarbonate (mEq./litre)*	*Blood-urea (mg./100 ml.)*	*Blood-glucose (mg./100 ml.)*
N.V.	< 1·0	> 3·2	< 3·2	< 4	4–14	< 3	6–10	140–265	< 10	< 13	137–148	4·0–5·0	101–106	25–29	35	68–120
1	1·7	3·1	3·5	13	20	3	17	283	16	13	135	3·5	104	21	18	64
2	0·8	2·8	4·1	7	30	0	12	258	19	13	135	4·2	108	21	28	116
3	1·0	3·2	3·4	8	18	0	8	245	6	12	130	3·9	104	27	9	74
4	0·6	3·1	4·2	7	..	..	7	..	..	..	..	..	..	..	30	96
5	1·0	2·6	3·1	8	..	5	38	246	..	26	..	..	..	..	28	..
6	0·7	3·2	2·5	1	4	0	11	237	9	12	147	5·1	103	27·8	18	80
7	1·9	2·7	4·2	4	18	0	22	280	26	15	140	2·9	109	27	12	60
8	1·6	2·4	3·4	15	18	4	11·8	330	23	14	133	3·6	109·2	24·5	19	79
9	1·7	3·4	3·0	8	14	0	28	240	17	12	133	4·0	104	28·4	12	82
10	0·8	3·0	2·8	0	14	..	20	197	17	13	145	4·0	103	29·4	21	79
11	0·6	2·9	2·9	0	10	..	20·5	191	16	12	150	4·3	108	29·9	12	72
12	1·2	2·8	4·1	5	16	..	24	255	..	12	140	3·7	103	25·9	19	120
13	2·6	3·6	4·2	2	6	..	80	251	..	15	138	3·6	166	25·9	..	76
14	1·3	3·1	2·4	3	10	0	11·4	220	..	15	136	3·3	101	26·2	34	87
15	4·8	2·7	6·0	26	24	5	19·2	200	10	17	143	3·6	107·9	29·6	22	84
16	0·5	2·9	3·3	4	8	..	22	294	10	14	140	4·7	110	23·5	31	85
17	0·3	2·8	2·6	3	8	0	20	..	..	..	..	..	..	..	30	75

serum-globulin level was over 3·5 gm. per 100 ml., with a marked increase in the gamma fraction. In seven of 11 patients bromsulphthalein retention was abnormally high, and in nine flocculation tests were positive. Investigations in Patient 13 were compatible with a diagnosis of biliary cirrhosis. Five patients (Nos. 3, 6, 10, 11, and 16) showed little biochemical evidence of liver disease, and the diagnosis was confirmed by needle liver biopsy. In Patient 15 recurrent neuropsychiatric exacerbations were associated with clinical and biochemical evidence of deteriorating liver function, and in Patient 7 progressive liver failure resulted in failure of treatment and ultimate death. The neuropsychiatric status, however, could not usually be related to changes in liver-function tests.

Other Investigations

Peripheral-vein ammonium levels (Table II) were usually raised, and the values reported are representative of numerous estimations. Levels varied widely from day to day, but normal readings were exceptional. During neuropsychiatric deterioration electrolyte, urea, and glucose levels in the blood (Table III), and cells, protein, glucose, and chloride in the cerebrospinal fluid, were usually normal. The cerebrospinal-fluid Wassermann and Kahn reactions were negative. Ammonium and glutamine levels in the cerebrospinal fluid were always raised.

Intolerance of Nitrogenous Substances

The 15 patients tested were all sensitive to oral nitrogenous substances (Table IV), and the degree of neuropsychiatric disturbance paralleled the amount of nitrogenous material in the diet. On ordinary ward diets gross neuropsychiatric disorder existed in every patient, and the disorder could be aggravated by higher protein feeding, critical amounts varying in the individual patient. Sixty gm. of protein daily was the upper limit of tolerance, deterioration occurring within a few days; Patients 7 and 17, with severe and progressive impairment of liver function, presented gross neuropsychiatric signs when given only 20 gm. of protein daily. Patients were usually sensitive to oral *dl*-methionine or ammonium chloride in doses of 10 gm. daily, and this test was useful in diagnosis. The critical total dose of *dl*-methionine varied between 11 and 76 gm., but two patients (Nos. 6 and 14) tolerated large doses with no adverse effect. Ammonium chloride in total doses of 8 to 66 gm. promoted neurological disturbance in the six patients to whom it was given. Fifteen patients were treated by restriction of dietary protein. An 'excellent response' in six patients indicates remission of neuropsychiatric disturbance and return to normal mental and physical activity. The five patients with a 'good response' experienced intermittent mild episodes of apathy or confusion, with tremor or other objective signs. The four patients who 'improved' exhibited constantly deranged neuropsychiatric function, but without gross personality change or antisocial behaviour. The latter nine patients still experienced episodes in which complete withdrawal of protein from the diet was necessary and oral chlortetracycline (2 gm. daily) was added, usually with benefit. Out-patient

progress was satisfactory; the patients appreciated the symptoms of impending deterioration, and excluded protein from their diet until improvement occurred. Except in Patients 7 and 15, in whom liver function was severely impaired, no

TABLE IV

Intolerance of Nitrogenous Substances and Response to Treatment

Patient No.	*Limit of protein tolerance (gm. daily)*	*Reaction to dl-methionine, and total dose*	*Reaction to ammonium chloride, and total dose*	*Response to treatment*
1	50	Severe, 20 gm.	Severe, 65 gm.	Excellent
2	50	,, 26 gm.	,, 26 gm.	Good
3	40	,, 32 gm.	,, 15 gm.	,,
6	40	None, 66 gm.	,, 66 gm.	Excellent
7	<20	Severe, 14 gm.	,, 8 gm.	Improved
8	40	,, 40 gm.	,, 10 gm.	Good
9	50	,, 11 gm.	..	Excellent
10	60	..	..	,,
11	40	Severe, 34 gm.	..	,,
12	50	Mild, 76 gm.	..	Good
13	50	..	..	Excellent
14	60	None, 70 gm.	..	Improved
15	40	Severe, 32 gm.	..	,,
16	40	..	..	Good
17	<20	..	..	Improved

relationship existed between sensitivity to various nitrogenous substances and the ultimate response to dietary protein restriction. This may reflect either the difficulty in establishing a satisfactory base-line before administration of the drugs (owing to the fluctuating neurological state), or the intelligence with which patients undertook their own management on discharge from hospital.

Discussion

The diagnosis is suggested by fluctuating neuropsychiatric disturbance with prominent motor disorder, supported by the presence of chronic liver disease, splenomegaly, and fetor hepaticus, and is confirmed by intolerance of dietary nitrogen and by characteristic changes in the electroencephalogram. In all our patients an extensive portal-systemic collateral circulation could be demonstrated, usually by portal venography. Biochemical investigations contribute little, although the finding of high blood-ammonium levels supports the diagnosis. Diagnostic difficulties arise in a patient who shows neurological disorder and little objective evidence of liver disease, and no less in one who is clearly suffering from portal cirrhosis, but is also exhibiting mental changes. Assessment of nitrogen tolerance is the most specific investigation. Dietary protein in excess of 60 gm. daily, or ammonium chloride or methionine in doses of 10 gm. daily, will usually induce a diagnostic deterioration. In mild cases confirmation by repeated electroencephalographic records is advisable, since little objective deterioration may occur with these doses. All such trials should be carried out with strict clinical control and repeated neuropsychiatric observation. Larger amounts of the drugs are contra-indicated, since severe reactions may occur, sometimes with dramatic suddenness. Restriction of dietary protein to 20 gm.

daily is usually followed by improvement, although sometimes delayed, and is an equally valuable test.

Patients in the present series had received various diagnostic labels; these included anxiety state, frontal-lobe tumour, narcolepsy, psychomotor epilepsy, multiple sclerosis, hysterical ataxia, depressive psychosis, cerebral arteriosclerosis, Wilson's disease, and Parkinsonism. The chronic organic reaction was characterized by personality change, mood disorder, and intellectual defect; these fluctuated in severity, and were essentially reversible. This clinical picture resembles any chronic toxic psychosis. The fluctuations differentiate it from the progressive organic dementias such as those accompanying cerebral arteriosclerosis, and from residual dementias following an acute insult such as carbon monoxide poisoning or cerebral trauma. Chronic barbiturate poisoning may be simulated. The chronic alcoholic patient with delirium tremens is more fearful and sleepless, with terrifying visual hallucinations. In one patient (No. 7) the intense visual imagery and hallucinosis, marked synaesthesia, and disturbance of visual perception, resembled the picture produced by the 'fantasticum' group of drugs, mescaline and lysergic acid diethylamide. The chronic mild disorder may be confused with depression and depressive stupor, for a fixed expression, diminution in spontaneous movements, loss of interest, psychomotor retardation, nocturnal insomnia, listlessness, and headache are common to both. Symptoms are also worse in the morning in both conditions. A depressed mood, moreover, can usher in this syndrome. Mood changes may resemble cyclothymia, and schizophrenic stupor may be simulated in patients who show catatonic episodes with mutism. The frequent release of latent functional psychoses adds to the diagnostic difficulties. This is a well-known occurrence in chronic toxic states, the type of reaction being related to the previous personality, and to intensification of personality trends. No constant relationship to the extent of the organic disorder was observed. Depressive reactions may occur early, dominating the clinical picture, or only at the height of stupor, or even when the patient is free from neurological signs. The psychiatric importance of the syndrome is emphasized by the fact that four patients in the present series were admitted to mental hospitals, and in other cases this event was avoided only by the care of devoted relatives. One of us recognized four patients with this syndrome in the course of three months in a mental hospital containing 1,000 beds. Havens and Child (1955) also described a recurrent manic reaction with confusion, necessitating admission to a mental hospital, in a patient of 64 years who had had a portacaval anastomosis. The patient is very liable to fall between the stools of various specialist interests. The psychiatrist is interested in the non-specific organic reaction, and may not consider underlying liver disease. The neurologist focuses attention on the interesting combination of an extrapyramidal and pyramidal lesion with flexor plantar responses, while the hepatologist, recognizing the cirrhosis, fails to elicit the neurological signs, or assumes that the patient is just 'queer' or an alcoholic. The patient may be seen for the first time in coma or in remission, adding to the diagnostic difficulty.

The electroencephalogram in hepatic coma has been well described by Foley, Watson, and Adams (1950) and Bickford and Butt (1955). Our findings agree with theirs. The electroencephalogram is not entirely specific for hepatic coma, similar tracings being found in some patients with epilepsy, with anoxic and metabolic disturbances of the brain, or with disturbed consciousness generally. The presence of bilateral slow waves adds diagnostic weight to an uncertain neuropsychiatric picture occurring in a patient with portal cirrhosis.

The size of the portal collateral circulation is said to be proportional to the portal venous pressure (Atkinson, Barnett, Sherlock, and Steiner, 1955); this did not always prove to be the case, for when the collateral circulation was sufficiently great the intrasplenic and occluded hepatic-vein pressures were normal. Such patients usually had one large collateral vein, commonly the umbilical or inferior mesenteric. They had constructed natural portacaval shunts of sufficient calibre to lower the portal venous pressure, and did not therefore suffer from bleeding oesophageal varices. The portal venous pressure had at one time presumably been high, and in Patient 6 this was shown by the loud abdominal venous bruit and thrill, which diminished as the portal venous pressure fell. Neurological changes are known to follow surgical portacaval anastomosis (McDermott and Adams, 1954), and Riddell (1955*a*) estimated the incidence as 10 per cent. Wooler (1955) believed that up to 30 per cent. of patients show some neurological deterioration after the operation, although only a small proportion of such cases become chronic. He suggested that the incidence depends on the size of the anastomosis and on the age of the patient. Such deterioration might be anticipated in patients with advanced liver disease, but liver function was relatively good in three of our four patients who had had portacaval anastomosis. Portal-vein thrombosis predisposes to the syndrome (Sherlock, Summerskill, White, and Phear, 1954). Hunt and Whittard (1954) assessed the incidence of portal-vein thrombosis in cirrhotic patients as 11 per cent., and incriminated it as a cause of acute neuropsychiatric disorder following portal-systemic anastomosis. Patency of the umbilical vein has not been recorded previously in association with portal-systemic encephalopathy, although Wollaeger and Shands (1945) described this venous anomaly in Wilson's disease in two patients, one of whom exhibited atypical neurological signs. Shunting of blood through a dilated inferior mesenteric vein has also not been previously reported with this syndrome. Less commonly the collateral circulation consisted of multiple small channels.

In most of our patients impairment of liver function was mild. This favoured the long duration of the neurological disorder, and occasionally necessitated needle liver biopsy for diagnosis of the cirrhosis. The question arises whether the syndrome can follow shunting of portal blood in the absence of liver disease. Animals with Eck's fistulae exhibit nitrogen intolerance (Baló and Korpássy, 1932), and a patient with only fatty infiltration of the liver suffered from this neuropsychiatric syndrome after undergoing portacaval anastomosis (McDermott and Adams, 1954). Since the liver deprived of its portal blood-supply probably cannot function normally, the point cannot be settled until more

sensitive tests of hepatic function are available. The importance of liver function was particularly evident in two of our patients, one of whom responded inadequately to treatment and deteriorated rapidly because of progressive liver failure, while the other suffered recurrent exacerbations of the nervous disorder with repeated episodes of jaundice and ascites.

All the patients were sensitive to changes in the amount of protein in the diet. The exact nature of the toxic substance derived from protein is uncertain, but, as an extensive portal-systemic circulation existed in every patient, it is probably present in portal blood and derived from the intestinal contents. A similar disorder occurs acutely in hepato-cellular failure without a portal collateral circulation, and the toxic factor is probably metabolized by the liver in normal circumstances. Dietary protein, ammonium chloride, and methionine cause exacerbations in this group of patients, while other ammonium compounds and urea can precipitate transient neurological disorder in patients with cirrhosis (Phillips, Schwartz, Gabuzda, and Davidson, 1952). Ammonium is the simplest nitrogenous substance which can be derived from all these compounds, and high ammonium levels are present in portal venous blood (Kirk, 1936). The synthesis of urea from ammonium is an important function of the liver (von Schröder, 1882; Krebs, 1952), and is impaired by liver disease or by an extensive portal collateral circulation (White, Phear, Summerskill, and Sherlock, 1955). Moreover, high ammonium values occur in the peripheral blood in hepatic coma (Traeger, Gabuzda, Ballou, and Davidson, 1954), but cannot be accurately related to the degree of neuropsychiatric disorder (Phear, Sherlock, and Summerskill, 1955). The brain has been shown to take up ammonium in hepatic coma (Bessman and Bessman, 1955), and possible derangements of cerebral metabolism due to ammonium intoxication have been discussed by Walshe (1951), Bessman and Bessman (1955), and Riddell (1955*b*). Alternatively, one or more other nitrogenous constituents of portal blood may prove to be important. The neuropsychiatric syndrome has been reproduced by giving methionine, without alteration in the blood-ammonium values (Phear, Ruebner, Sherlock, and Summerskill, 1956). Fetor hepaticus, a constant finding in our patients, is also thought to originate from the intestines. The 'auto-intoxication' theory of mental illness was popular twenty years ago. It was postulated that, when hepatic function was disturbed, products derived from bacterial action on protein in the gut gained access to the systemic circulation and so affected the brain (Quastel, 1932). This theory has now been confirmed, although the psychiatric illness of portal-systemic encephalopathy is an organic reaction and not solely the functional psychotic state suggested by earlier workers.

When the diagnosis has been confirmed, the limit of protein tolerance must be assessed. This is ideally carried out in a metabolic ward, with full information of nitrogen balance, caloric intake, body-weight, and neuropsychiatric state. Satisfactory diets contain 30 to 60 gm. of protein, which with an adequate caloric intake are compatible with nitrogenous balance. The patient and his family must realize the dangers of any deviation from this diet. They should be able to recognize signs of impending deterioration, and instructed to withdraw dietary

protein immediately, administering only glucose drinks. Since there is evidence that the toxic factor is of intestinal origin and related to bacterial action on protein, an enema and a short course of chlortetracycline (2 gm. daily for two days) is also given. Failure to improve rapidly is an indication for admission to hospital, as the relapse may have resulted from a complication such as gastro-intestinal haemorrhage. Patients are also warned to avoid alcohol and certain drugs such as morphia, which are known to be tolerated badly. The results of treatment are always beneficial, and often spectacular. Despite gross neuro-psychiatric disorder of two or three years' duration, patients have returned to lives of normal physical and mental activity without having suffered permanent cerebral damage. Long-term treatment is based on protein restriction, and we have observed five patients who have taken diets containing 40 to 50 gm. of protein for one to one and a half years without the development of hypoproteinaemia or deterioration in general health. The protein may be better tolerated if it is given in small amounts at frequent intervals. McDermott, Adams, and Riddell (1954) advocated the long-term use of glutamic acid in such patients; our experience with this drug has been equivocal. Small daily doses of chemotherapeutic agents might be expected to be beneficial, but this has not proved to be the case in our experience. It is unlikely that further advances in treatment will be possible until the toxic agent and its effect on cerebral metabolism have been clearly identified.

We are indebted to Dr. D. H. Brinton for allowing us to include Patient No. 4; to Dr. N. F. Coghill, Dr. F. Avery Jones, Dr. A. K. M. Macrae, and Mr. Geoffrey Wooler for referring patients to us; and to Dr. Gerald Parsons-Smith for reports and advice on electroencephalographic changes. We wish to thank the Medical Research Council for a personal grant to one of us (E.A.D.).

Summary

Seventeen patients with chronic liver disease presented an intermittent neuro-psychiatric disturbance for periods of six months to six years.

The chronic organic reaction was characterized by personality change, mood disorder, and intellectual defect. These fluctuated in severity, and were essentially reversible. The acute organic reaction was shown by delirium with clouding of consciousness. Twelve patients showed functional psychotic or psychoneurotic reactions. The neurological changes included tremor and exaggerated tendon-reflexes, usually with flexor plantar responses; there was evidence of widespread neurological disturbance. The electroencephalogram showed the picture described in impending hepatic coma.

In 15 patients an extensive portal-systemic collateral circulation could be demonstrated, usually by percutaneous trans-splenic portal venography. In the other two patients a bleeding tendency precluded this procedure. In five patients the portal vein was occluded by thrombosis and the entire portal blood-stream diverted into collateral channels, and in two of these patients the inferior mesenteric vein was distended to form a single large collateral channel.

In two patients the umbilical vein was widely patent. Four patients had an effective surgical portacaval anastomosis. In four patients the collateral circulation was extensive without a single major vessel. When the collateral channel was a single major communication, whether natural or surgically constructed, the portal venous pressure, as measured by the intrasplenic pressure, was usually normal.

The patients usually showed some of the clinical and biochemical features of chronic liver disease, although in some instances these changes were minimal. In every patient the blood-ammonium level was raised at some time. All had splenomegaly and fetor hepaticus.

Fifteen patients were tested with a high-protein diet, and all deteriorated. Six deteriorated on being given ammonium chloride, and some when given oral methionine. The limits of dietary protein tolerance were from less than 20 gm. to 60 gm. All patients benefited by protein restriction, and in six the therapeutic result was considered excellent.

It is suggested that a toxic nitrogenous substance or substances are absorbed from the intestine and reach the systemic veins, and hence the brain, through portal collateral channels, so causing the cerebral disturbance.

The diagnosis and psychiatric importance of this syndrome are discussed.

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FIG. 3. Portal venogram of patient No. 1. The portal vein is occluded, and all the contrast medium is diverted into collateral channels

FIG. 4. Portal venogram of patient No. 8. The portal vein is occluded, and the contrast medium is diverted into a greatly dilated inferior mesenteric vein

FIG. 5. Portal venogram of patient No. 3. Functioning portacaval anastomosis. The splenic and portal vein are filled and of normal calibre, but no contrast material reaches the liver

FIG. 6. Portal venogram of patient No. 7. A very large amount of contrast medium is diverted into a large umbilical vein, which is filled from the left branch of the portal vein and passes towards the iliac veins. Later films showed filling of the inferior vena cava

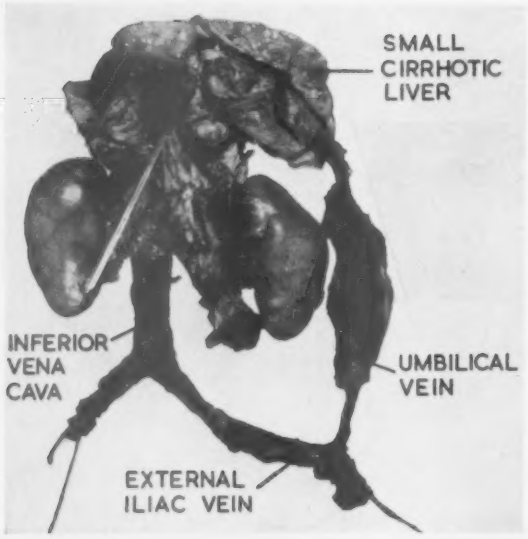

FIG. 7. Autopsy dissection from patient No. 7. The dilated umbilical vein has been injected with Indian ink, and is seen to arise from the left branch of the portal vein and to join the right external iliac vein

FIG. 8. Portal venogram of patient No. 16. The portal vein is patent. There is an extensive collateral circulation, mainly through the left gastric and oesophageal veins, but also through some lumbar veins, the left suprarenal vein, and the inferior vena cava. The intrahepatic radicles are distorted

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NEUROPATHY IN PERIPHERAL VASCULAR DISEASE[1]

Its Bearing on Diabetic Neuropathy

By E. C. HUTCHINSON and L. A. LIVERSEDGE

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The importance of peripheral vascular disease in the clinical picture of diabetic neuropathy has long been a matter for speculation, and one on which widely divergent views have been expressed. Woltman and Wilder (1929) believed that the neural changes were entirely due to pathological changes in the peripheral vessels, a view which has received some support (Jordan, 1936; Dry and Hines, 1941). Martin (1953), however, during a clinical review of 150 cases of diabetic neuropathy, studied in detail the peripheral vascular function in 20 of the patients, as judged by oscillometry and skin-temperature tests following the administration of tolazoline. His results led him to think that no fundamental role could be attributed to a vascular disorder in the development of diabetic neuropathy. A similar opinion has been expressed by Matthews (1955). It occurred to us that additional information on the problem might be obtained by a study of the neurological abnormalities to be found in a random selection of patients suffering from known peripheral vascular disease, uncomplicated either by diabetes mellitus or any other cause of neurological disorder.

Patients Studied

The patients examined in this investigation were attending the Department of Surgery of the Manchester Royal Infirmary for treatment of peripheral vascular disease, and all were suffering from intermittent claudication. Partial selection was practised, in that we excluded all patients with diabetes mellitus or coexisting neurological disease, and also all who had gangrene of the extremities, for it was felt that the latter condition introduced the possible complicating factor of infection. The details of previous treatment, the presumptive site of the vascular occlusion as determined by oscillometry, and the clinical severity of the disease as assessed by the claudicometer, were made available to us at the conclusion of our investigation.

Results

Ninety patients were examined, and of these 53 (58·8 per cent.) showed evidence of neurological abnormality in the lower limbs which we considered to be due to the underlying vascular disease. The abnormalities encountered fell into two groups (see Table). The first group of 11 patients consisted of those complaining of subjective sensory disturbances without abnormal signs. In the

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second group, comprising 42 patients, abnormal neurological signs were detected, both with and without subjective symptoms. The ages of the patients examined ranged from 40 to 80 years (Fig. 1). Although the group from 71 to 80 years contains a higher proportion of patients with abnormal neurological

Neurological Abnormalities in Peripheral Vascular Disease

	Number of patients
Patients examined	90
Patients with neurological abnormality	53
Sensory symptoms without signs	11
Objective neurological signs	42
Reflex alteration (19)	
Muscle wasting (5)	
Muscle weakness (1)	
Sensory impairment (31)	

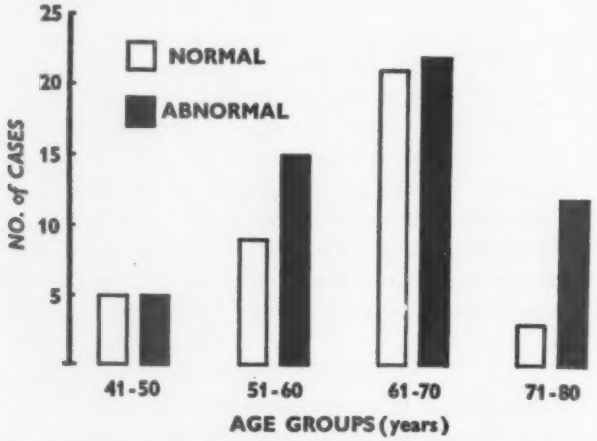

FIG. 1. Age distribution of the patients examined. The neurologically normal and abnormal in each decade are contrasted.

findings, we cannot discern any significant correlation between age and neurological abnormalities.

Alteration in reflexes. Diminution or absence of tendon-reflexes in the lower limbs was found in 19 patients. Although the advanced age of some of these patients might suggest that such a finding could be accounted for on this ground alone, we did not feel that this was an adequate explanation, since in all but four of these patients other neurological abnormalities were also present; in two of four patients in whom both ankle-jerks were absent, sensory loss was also detectable in both limbs, a third showed sensory loss in one limb, and the fourth a global wasting of one limb. In the remaining 11 patients only one ankle-jerk was either appreciably diminished or absent. This alteration constantly occurred in the limb more severely affected by claudication, and was found in association with sensory loss in six patients, with muscle wasting in four, and with a diminished knee-jerk in the same leg in two others.

Muscle wasting. Demonstrable wasting of muscles of the lower limbs was noted in five patients. Never gross, the wasting involved either the whole lower limb or the muscle-groups below the knee, but in all five patients the wasting was global rather than confined to single muscle-groups. The striking feature was the virtual absence of any motor weakness, either subjectively or as found on formal testing. In four of the five patients there was in addition a diminution

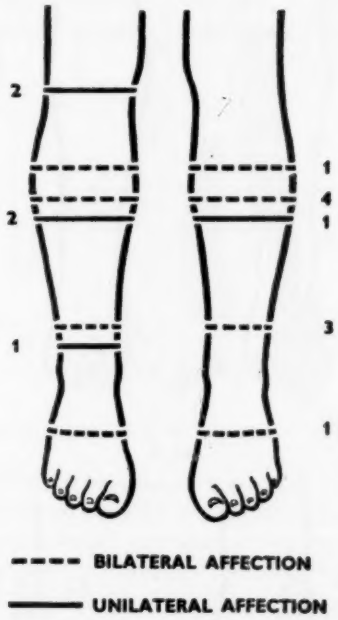

FIG. 2. In 15 patients the sensory loss was of the 'stocking' type. The extent of the disorder is shown. The figures indicate the number of patients affected at each level.

or absence of reflexes in the wasted limb, but only in one was sensory loss detected.

Muscle weakness. A complaint of muscle weakness was encountered only once in this series. The history of this patient is of some interest, and worth recording more fully.

Case 21. A month before examination the patient, a man of 40 years, was seized with a severe pain in the left leg. The pain persisted for seven days, after which he was able to walk again. He then noted that, in addition to pain of moderate severity in the left calf on walking 80 to 100 yards, he developed a left foot-drop and numbness over the lateral aspect of the lower leg. These symptoms were relieved by a short rest, only to recur with further exertion. Examination revealed a left femoral occlusion, some weakness of the left anterior tibial and peroneal muscles, and impairment of pain and light touch

sense over the cutaneous area supplied by the lateral popliteal nerve. We interpreted these signs as indicating an 'ischaemic lateral popliteal nerve palsy', and in the next two months the weakness and numbness resolved, leaving pain in the calf on walking as the only symptom. The susceptibility of the lateral

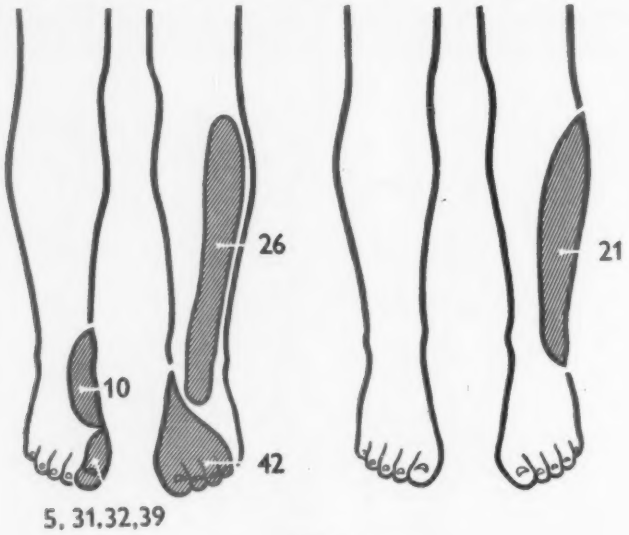

FIG. 3.

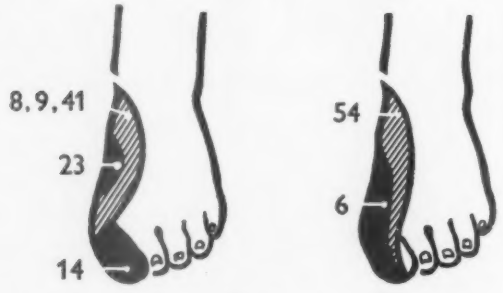

FIG. 4.

FIGS. 3 and 4. In 16 patients the sensory disturbance was localized. The distribution in each case is shown; the hatching and shading are only to indicate different topography, and do not relate to intensity of the disturbance. The numbers refer to individual cases.

popliteal nerve to ischaemia has been observed by Ferguson and Liversedge (1954).

Sensory abnormalities. A disturbance in the sensory function of the peripheral nerves producing subjective symptoms, objective sensory loss, or a combination of both, was the commonest abnormality encountered, and was noted in 42 of the 90 patients. In almost all cases this disturbance occurred in the limb more severely affected by peripheral vascular disease. The subjective

sensory features displayed a fairly constant pattern, independent of the presence or absence of signs. The commonest symptom was an ill-defined sensation of 'pins and needles' or 'tingling' in the foot or lower third of the limb. Less common was the numbness described by seven patients, and an interesting feature in four of these was an increase in this numbness on exertion and subsequent relief by rest, apparently a neural counterpart of intermittent claudication. Other more positive sensations were variously described as itching, pricking, and burning, in circumscribed areas of skin, and in three patients intense pain

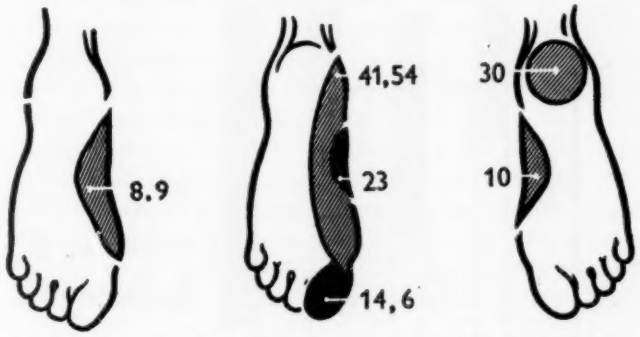

FIG. 5. Extension on to the sole of the sensory loss displayed in Figs. 3 and 4.

was noted to occur in localized areas over the foot in response to the stimulus of heat, cold, and touch respectively. In certain cases these areas of localized sensory symptoms corresponded very clearly with an area of objective sensory impairment. The most striking sensory symptom, though the least common, was experienced by three patients, who described intermittent severe stabbing pains similar to those encountered in tabes dorsalis.

The distribution of the areas of objective sensory impairment is shown in Figs. 2 to 5. Although all the changes were found below the knee, two types may be distinguished. In 15 patients the distribution was of the 'stocking' type, either bilateral or unilateral, and, although the absence of pathological evidence has prevented the absolute determination of the site of vascular occlusion, one patient who clinically showed occlusion of the aorta, and another who showed occlusion of the external iliac artery, showed 'stocking' sensory loss only up to the knee (Fig. 2). The remaining patients showed localized areas of sensory loss over the areas indicated in Figs. 3, 4, and 5. These areas were most frequently found in the great toe or the inner side of the dorsum of the foot, extending for a short distance on to the sole. In the main, however, they did not correspond to the accepted anatomical distribution of cutaneous nerves. The type of sensory loss varied within broad limits. In the great toe, especially when the circulation was sufficiently impaired to produce change in the colour of the skin, the anaesthesia was dense. Elsewhere the loss entailed only a hypalgesia and hypaesthesia, although of sufficient depth to allow easy determination of the boundaries. In five instances, within the area of hypalgesia, small areas

of intense hyperalgesia were encountered. Finally, we were unable to establish any constant relationship between the subjective symptoms and the type of sensory loss, but in a few cases the episodic nature of the sensory symptoms suggested that the neural lesion was capable of full recovery.

Discussion

In presenting this analysis of the results of detailed neurological examination in these patients, we do not wish to place undue emphasis on the neurological

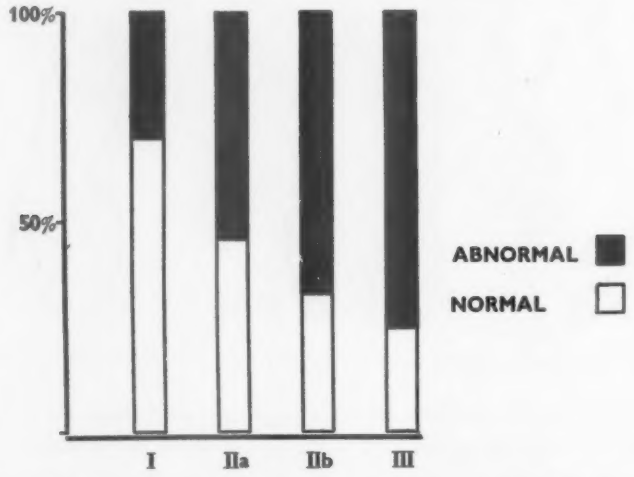

FIG. 6. The relative proportions of neurologically normal and abnormal patients in each group of claudicants.

Classification of groups: I. Pain of claudication passes off as walking continues. IIa. Pain of claudication persists at a durable level despite continued walking. III. Pain of claudication develops rapidly and becomes increasingly severe. Patient compelled to stop within 200 yards. IIb. Includes patients between Groups IIa and III.

abnormalities we encountered. It is important to record that the symptoms of peripheral vascular disease overshadowed the neurological symptoms, since, with the single exception of one patient with a lateral popliteal palsy, it was nearly always necessary to inquire specifically for neurological symptoms; they were rarely volunteered spontaneously by the patient. Indeed, the most striking feature has been the slightness of the neurological symptoms and signs in spite of advanced peripheral vascular disease. The incidence of neurological abnormalities is rather higher in the present series than in the series of 145 patients examined by Mufson (1952). He found that 43 per cent. of his patients showed abnormal signs, with a high preponderance of sensory abnormalities.

Lacking the anatomical details of the precise distribution and extent of the disease in the peripheral vessels, we did not expect, nor did we find, a close correlation between the presumptive 'clinical' site of the vascular occlusion and the neurological signs. There is, however, a relationship between the clinical

severity of the vascular disease and the incidence of neurological abnormalities (Fig. 6). The pathological substrate of ischaemic neuropathy has been well established by Priestley (1931) in his study of the peripheral nerves in arteriosclerotic limbs. There he stressed the higher incidence of Wallerian degeneration and fibrosis in the distal, as compared with the proximal, part of the nerve, and a degree of correlation between the vascular and neural change. The sensory loss in the great toe, which we found in seven patients, was usually associated with change of colour in the skin of the toe, and was considered to be due to involvement of the digital nerves by ischaemia. We regard the 'stocking' loss, either bilateral or unilateral, as an expression of ischaemia of the major nerve trunks, for it has been known since the classical studies of Lewis, Pickering, and Rothschild (1931) that the sensory fibres are the most sensitive to the effects of ischaemia. But neither of the above explanations suffices to account for the patchy areas of sensory loss over the dorsum of the foot and the sole, found in 11 patients, which, as we have mentioned, do not correspond to the accepted anatomical distribution of peripheral nerves. Scattered lesions in the major nerve trunks are known to occur, and, since there is evidence that the functional topography of the cutaneous nerves is not maintained within the major nerve trunks (McKinley, 1921), such lesions may account for the areas of sensory loss.

A study of the findings we have described will emphasize the distinction between the neurological picture seen in these patients and the accepted clinical picture of diabetic neuropathy. The neurological abnormalities are confined to the regions supplied by the diseased vessels, and there was no evidence of involvement of the autonomic system, so frequently seen in diabetes mellitus. But perhaps the most striking feature was the difference in degree of the neural damage as assessed clinically in the two conditions. In diabetic neuropathy the signs are decisive and the symptoms prominent, whereas the neurological abnormalities in peripheral vascular disease form a secondary part of the whole clinical picture. It seems possible, however, that the high incidence of peripheral vascular disease in elderly diabetics may lead one to attribute a small proportion of the neural signs to 'ischaemic neuropathy' as well as to the diabetic state.

Our thanks are due to Professor A. M. Boyd, of the Department of Surgery, for permission to examine these patients, who were under his care; also to Mr. K. Bloor, of the Department of Surgery, for his co-operation in providing us with the clinical details.

Summary

Ninety patients with peripheral vascular disease have been examined, and the neurological abnormalities encountered in 53 patients are described.

Attention is drawn to the relatively mild nature of the neural change in the presence of advanced peripheral vascular disease.

The distinction between the neural changes produced by vascular disease and diabetic neuropathy is emphasized.

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AN INVESTIGATION OF PROLONGED INSULIN RESISTANCE IN A CASE OF DIABETES MELLITUS[1]

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In cases of diabetes mellitus that have become resistant to insulin the phenomenon has been attributed to causes such as the production of excessive quantities of insulin-antagonizing hormones, an abnormally fast rate of insulin destruction, or the formation of antibodies neutralizing insulin. These matters have been discussed at considerable length by Smelo (1948) and Davidson and Eddleman (1950). The subject of the present investigation received about 260,000 units of insulin during a period of 18 weeks in hospital, and required 600 units daily from the date of discharge until her death nine months later. The patient was a middle-aged diabetic, whose disease had followed an uneventful course for many years. An apparently trivial episode, a skin infection, led to the development of profound insulin resistance. Beginning this investigation with the assumption that the patient's blood might contain some insulin-neutralizing factor, we were surprised to discover instead that the blood-serum lowered the blood-sugar concentration in rats. So far as we are aware, the only published report indicative of such an abnormally high concentration of circulating insulin is that of Davidson and Eddleman (1950), who produced convulsions in mice by injecting the serum of an insulin-resistant patient. The present paper shows evidence for the conclusion that the blood of our patient contained a large amount of insulin.

Description of the Case

The patient was an obese woman (age, 57 years; weight, 192 lb.; height, 61 in.) whose diabetic condition was discovered in 1940. At that time glycosuria was controlled with 40 units of insulin per day. After 12 years without insulin therapy, the patient was given 35 units daily during the treatment of a furuncle on the hand. A month later insulin resistance developed, and increased until 500 units daily were insufficient to control the diabetic state. On May 1, 1952, the patient was admitted to Dunedin Hospital in diabetic coma. The blood-sugar was 430 mg. per 100 ml., and the urine contained glucose ++++, acetone ++++, and albumin +. Coma was controlled in 24 hours by administration of 3,000 units of insulin and seven litres of isotonic saline and glucose. Subsequent physical examination revealed a blood-pressure of 140/100 and mild hypertensive vascular changes in the optic fundi. Intertrigo, with patchy

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cutaneous necrosis, was present on the lower abdomen, perineum, and thighs. Throughout her stay in hospital glycosuria was controlled with soluble insulin, administered four-hourly in accordance with the results of urine tests. A glucose-tolerance test showed that the renal threshold was operating at a blood-glucose concentration of approximately 190 mg. per 100 ml. After recovery from coma the patient was maintained on 2,000 units of insulin daily, but the requirement increased, reaching a maximum in the fourth week and exceeding an average of 4,000 units a day (Fig. 1). The largest quantity given in a single day was 5,000

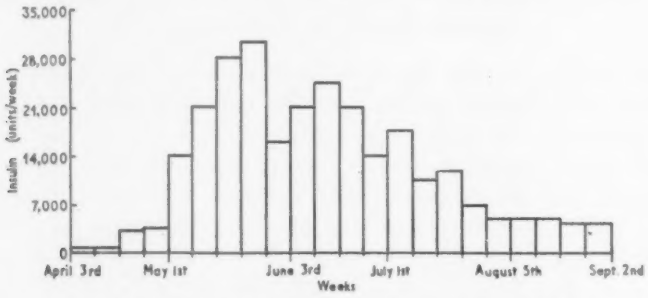

FIG. 1. The histogram shows the weekly dosage of insulin before admission to hospital on May 1, 1952, and the subsequent weekly dosage until the patient left the hospital.

units. In the fifth week the insulin requirement began to decline (Fig. 1); and in the 19th week, when the patient chose to leave hospital, she was receiving 600 units daily. Infections accompanied the ascending phase of the insulin-resistant state. During her second week in hospital an abscess developed in the thigh, and in the third week otitis externa and pyelonephritis. In each instance a coagulase-positive staphylococcus was found, and the condition treated effectively with penicillin and streptomycin.

Hospital laboratory investigations gave results within normal limits for the blood-cell count, blood non-protein nitrogen, serum alkaline phosphatase, serum-bilirubin, thymol-turbidity test, and ketosteroid excretion. Albumin in the urine amounted to 0·2 to 0·5 gm. per day. The electrophoretic pattern of the serum-proteins was abnormal (see page 281). There was no clinical or radiological evidence of hyperpituitarism, and no clinical evidence of adrenal or thyroid dysfunction. There was no conclusive evidence of allergy, or of immunity to insulin. Intracutaneous (forearm) injection of four units of insulin (Paley, 1949) was followed by the formation of a weal 1 cm. in diameter, but the Prausnitz-Küstner reaction, and precipitin tests by the direct and by the collodion-particle method (Cannon and Marshall, 1940), were negative.

The patient remained well for nine months, receiving daily 600 units of soluble insulin in two injections, but eventually returned to hospital complaining of severe retrosternal pain, and died soon after admission.

Post-mortem examination. The heart (460 gm.) was enlarged, hypertrophy being greater in the left ventricle. The aorta, and to a lesser extent the aortic

valve and pulmonary artery, were atheromatous. The coronary arteries showed patchy atheroma and calcification, and the calibre of the anterior descending branch was considerably reduced near its origin. The trachea and bronchi were congested, and the lungs moderately oedematous. The liver (2,820 gm.) was enlarged, and the cut surface smooth. Central and mid-zone fatty infiltration was present. The pancreas (95 gm.) appeared normal. Histological examination suggested some interstitial fibrosis, with diminution of islet tissue, in the sections examined. The kidneys were considerably scarred. Patchy collections of inflammatory cells were present in the wall of the renal pelvis and throughout the parenchyma. Mild degrees of arteriolar sclerosis and intercapillary glomerulosclerosis were observed. The adrenals were normal. The thyroid was somewhat enlarged and nodular. Permission to examine the cranial contents was refused. Death was attributed to insufficiency of coronary blood-flow due to atheroma of the vessels.

Carbohydrate tolerance and insulin sensitivity. Various tests were performed while the diabetes was kept under control with 2,000 to 4,000 units of insulin daily. The diet was calculated to provide approximately 1,800 calories (protein, 86 gm.; carbohydrate, 164 gm.; fat, 86 gm.). A *glucose-tolerance test* was carried out by withholding insulin for 24 hours and food for 12 hours before 50 gm. of glucose were given orally. The blood-sugar level rose progressively from 100 mg. to 250 mg. per 100 ml. during a three-hour period. A *fructose-tolerance test* (59 gm. of fructose orally) performed under the same conditions gave a curve characteristic of the diabetic state (Miller, Drucker, Owens, Craig, and Woodward, 1952). *Insulin sensitivity tests* were carried out after similar preparation, the absence of ketonuria being established. In one test soluble insulin (800 units), given intravenously, lowered the blood-sugar from 410 mg. to 350 mg. per 100 ml. during the first hour, after which the level rose progressively. Three brands of commercial insulin gave essentially the same results. The effects of withholding insulin were investigated on several occasions. When the blood-sugar had been rendered normal and the urine free from glucose, insulin could be discontinued for 28 hours before glycosuria recurred, and the glycosuria did not become severe until 48 hours had elapsed. On one occasion, when hypoglycaemia was induced with insulin and then the blood-sugar concentration restored to normal by intravenous administration of 20 gm. of glucose, followed by a further 95 gm. during the next five hours, there was a recurrence of hypoglycaemia, indicating that insulin exercised an unusually prolonged action.

These observations demonstrated a sluggish response to insulin, and suggested that the patient's blood might contain a concentration of insulin large enough to be detected in an anaesthetized-rat preparation, which had been devised and used for another purpose.

Effect of the patient's serum on the blood-sugar level of rats. Wistar rats, starved three to four hours, were anaesthetized and prepared in the way described by Todd (1954). The patient's serum (1·5 ml. per kg. rat body-weight) was injected slowly (taking one minute) into the long saphenous vein, and the changes in blood-sugar level followed for one to two hours. Blood-sugar was estimated

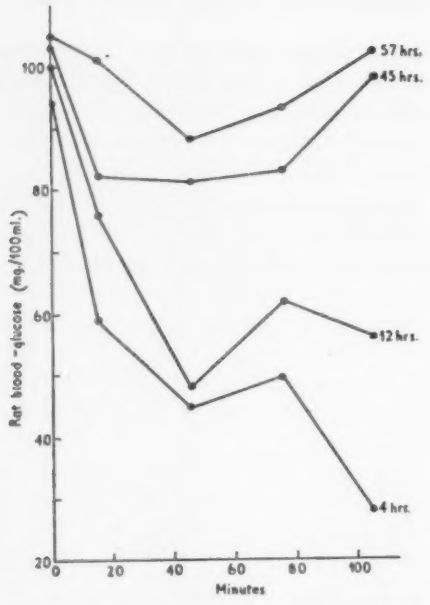

FIG. 2. The effect of the patient's serum on the blood-sugar level of rats at succeeding intervals (hours) after the suspension of insulin therapy. The rats received 1·5 ml. of the patient's serum per kg. rat body-weight, injected intravenously.

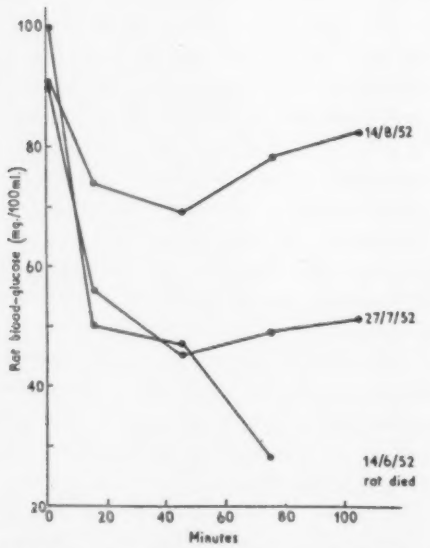

FIG. 3. The effect of the patient's serum on the blood-sugar level of rats in relation to insulin dosage. The approximate level of the average daily insulin dosage may be seen by referring the calendar dates to Fig. 1.

colorimetrically by the method of Somogyi (1952) and Nelson (1944). Samples of the patient's serum, taken when the insulin dosage was 2,000 units a day, and injected into rats, caused a profound hypoglycaemia, which was fatal in about one hour unless the blood-sugar level was restored by injection of glucose. When insulin was withheld from the patient there was a progressive decline in the hypoglycaemic action of the serum (Fig. 2). The samples taken 45 and 57 hours after

TABLE I

Hypoglycaemic Effects of the Patient's Serum to which Insulin had been Added

Sample	*Time since patient received last dose of insulin (600 units) (hrs.)*	*Time after injection into the rat*				
		0	*15*	*45*	*75*	*105 min.*
		Rat blood-sugar (mg./100 ml.)				
Patient's serum . . .	4	100	59	44	50	28
Patient's serum . . .	12	94	76	48	62	56
Patient's serum + insulin . .	12	92	32	34	36	47
Patient's serum . . .	45	103	82	81	83	98
Patient's serum + insulin . .	45	98	53	42	52	82
Patient's serum . . .	57	105	101	88	93	102
Patient's serum + insulin . .	57	93	48	33	45	61
Normal human serum + insulin .	..	100	50	44	65	99
Glucosine-saline + insulin . .	..	90	38	31	67	89

Rats were starved for three to four hours before the experiment, and prepared by the method of Todd (1954). Glucose-saline contained 0·1 gm. of glucose per 100 ml. of normal saline. The quantity of serum or glucose-saline injected intravenously was 1·5 ml. per kg. rat body-weight. The concentration of added insulin was 0·5 unit per ml.

the last injection of insulin had little hypoglycaemic action in the rat. These experiments are consistent with the view that the patient's blood contained a large amount of insulin, which was capable of exerting its characteristic effect on the blood-sugar level of the rat. Control experiments with normal human sera, and with the sera of diabetic patients receiving up to 50 units of insulin daily, had no significant effects on the blood-sugar level of rats. Dialysis of the serum against phosphate-buffered (pH 7·4) isotonic saline for 24 hours at 2° to 3° C. did not reduce its hypoglycaemic action. As the insulin dosage was reduced, the hypoglycaemic effect of the patient's serum diminished (Fig. 3). The possibility of the patient's serum binding or inactivating insulin was examined by adding insulin to samples of the serum used in the experiments of Fig. 2. The results are shown in Table I, which includes some control experiments with normal serum and glucose-saline. These experiments do not support the hypothesis that the patient's serum was able to bind or otherwise inactivate insulin. To test the possibility that whole blood might inactivate insulin, a sample was withdrawn from the patient 17 hours after the last insulin dose, heparinized, and incubated with insulin (0·5 unit per ml.) for seven hours at 38° C. The plasma was separated by centrifugation and injected into the rat intravenously. There was no significant reduction in the effect of the insulin.

Effect of the patient's serum on glycogen synthesis in the isolated rat diaphragm. The conclusion that the patient's blood contained a considerable amount of circulating insulin was supported by experiments on the rat hemi-diaphragm carried out with the technique of Stadie, Haugaard, Marsh, and Hills (1949). The hemi-diaphragms were immersed in 0·5 ml. of the patient's serum at 25° C., rinsed thoroughly in normal saline, and incubated in glucose-phosphate-saline

TABLE II

Glycogen-formation in the Rat Hemi-Diaphragm

(Method of Stadie, Haugaard, Marsh, and Hills (1949))

Specimen (0·5 ml.)	*Time of contact with diaphragm at 25° C. (min.)*	*Weight of hemi-diaphragm (mg.)*	*Glycogen (as μM. of glucose per mg. dry-weight of diaphragm)*
Normal human serum . .	15	156	6·10
Patient's serum . . .	15	136	11·40
Normal human serum . .	120	226	2·45
Patient's serum . . .	120	196	7·70

The patient's serum was taken four hours after the last injection of insulin (600 units).

TABLE III

Hypoglycaemic Effect of Serum-Protein Fractions

(Anaesthetized-rat preparation (Todd, 1954))

Protein fraction	*Time after injection*				
	0	*15*	*45*	*75*	*105 min.*
	Rat blood-sugar (mg./100 ml.)				
a. Fractions II+III	93	85	75	57	34
b. Precipitate (pH 5·3) from supernatant of fractions II+III	98	96	95	88	80
c. Fraction III	79	62	34	44	40
d. Precipitate from fraction II . . .	85	88	90	93	100

Precipitates *b*, *c*, and *d* were dissolved in glucose (0·1 gm./100 ml.)-normal saline. Rats received 1·5 ml. of dissolved fraction per kg. body-weight, injected intravenously.

as described by Stadie, Haugaard, Marsh, and Hills. The specimen of serum was obtained four hours after the last dose of insulin (600 units). The control hemi-diaphragms were treated in the same way with normal human serum. The results (Table II) show that the patient's serum stimulated the formation of glycogen in the isolated rat diaphragm, imitating the well-known effect of a solution of insulin.

The insulin activity of serum-protein fractions. The distribution of insulin among the proteins of the patient's serum was determined, and compared with the distribution obtained after the addition of insulin (prepared from a commercial sample by crystallization at pH 5·3) to normal serum. The methods of Cohn, Strong, Hughes, Mulford, Ashworth, Melin, and Taylor (1946) and of Oncley, Gurd, and Melin (1950) were used to separate the protein fractions. The serum was collected while the patient was receiving 1,200 units of insulin daily. Fractions II+III of Cohn, containing principally the γ-globulins and β_1-lipo-

proteins, were precipitated from 10 ml. of serum and found to contain much insulin (Table III*a*). The alcoholic supernatant from fractions II+III was adjusted to pH 5·3 (iso-electric point of insulin), but the small precipitate obtained had no hypoglycaemic activity (Table III*b*). The γ-globulin (II) was extracted from the precipitate II+III, and fraction III taken up in glucose-saline solution (Table III*c*). A further fraction was prepared from the γ-globulin

TABLE IV

Hypoglycaemic Effect of Protein Fractions form Normal Human Serum to which Insulin was Added

(Anaesthetized-rat preparation (Todd, 1954))

Protein fraction	*Time after injection*				
	0	*15*	*45*	*75*	*105 min.*
	Rat blood-sugar (mg./100 ml.)				
a. Fractions II+III	93	62	48	41	42
b. Precipitate from the supernatant containing fractions IV+V+VI . . .	85	65	71	74	81

The fractions were prepared from 10 ml. of normal human serum, to which 6 units of insulin were added. The precipitate containing fractions II+III was dissolved in 2·0 ml. of glucose (0·1 gm./100 ml.)-normal saline. The supernatant containing fractions IV+V+VI was adjusted to pH 5·0 with 1·0 M-acetate buffer, and the precipitate dissolved in 1·0 ml. of glucose-saline. Rats received 1·5 ml. solution per kg. body-weight, injected intravenously.

(II) by precipitation with 25 per cent. (v/v) alcohol at pH 5·3 (Table III*d*). It will be seen that the insulin is associated with fraction III. The experiments were repeated later, when the patient was receiving 700 units of insulin daily. Again the insulin activity was found in fraction III, and was absent from the Cohn fractions II and IV+V+VI. When normal human serum to which insulin had been added was fractionated, the insulin was precipitated in fractions II+III, but the supernatant contained an appreciable amount which could be precipitated at the iso-electric point of insulin (Table IV). The volume of the precipitate II+III was noticeably smaller than that of the same fraction obtained from the patient's serum. When the fractionation procedure was carried out with a neutralized aqueous solution of insulin, the insulin was not precipitated under the conditions used to obtain fractions II+III from serum.

Changes in the electrophoretic pattern of the serum-proteins. The total serum-protein was estimated by the method of Levin and Brauer (1951), and the electrophoretic patterns were determined in a Hilger-Tiselius apparatus and analysed by conventional methods. The results are given in Table V. The total protein is not greatly depleted. The striking features of the first sample (28.5.52), taken when the insulin requirement was 4,100 units per day, are the hypoalbuminaemia, the low albumin/globulin ratio, and the elevated proportions of the α- and γ-globulins. Later, when the insulin requirement diminished, there was a progressive increase in the albumin and a decrease in the α- and γ-globulins, and the β-globulins increased to higher proportions as the rest of the protein spectrum moved towards normal.

Lewis, Schneider, and McCullagh (1944), Schneider, Lewis, and McCullagh (1946), Luetscher (1947), and Marrack and Hoch (1949) have discussed the changes in the electrophoretic pattern of plasma- or serum-proteins in uncontrolled diabetes mellitus and in patients with diabetic retinitis. In mild uncontrolled diabetes mellitus without vascular complications the protein spectrum may be normal, although the total protein is slightly decreased; but in

TABLE V

Electrophoretic Analysis of the Serum-Proteins

Conditions: veronal buffer, pH 8·6, ionic strength 0·2

		Percentage of total protein (ascending) pattern)						
		Albumin	*Globulins*				*Albumin/ globulin ratio*	*Insulin dosage (units/ day)*
Date	*Total protein (gm./100 ml. serum)*		α_1	α_2	β	γ		
28.5.52	6·16	19·4	10·2	15·6	15·5	39·1	0·24	4,100
22.7.52	6·47	33·5	6·7	15·1	19·5	25·2	0·50	1,300
12.9.52	7·44	43·5	4·6	11·0	20·0	20·9	0·77	700

more severe diabetes the albumin may be diminished and the β-globulin considerably increased. After diabetic control is established the protein spectrum tends to revert to normal, unless there are concomitant vascular lesions, when low albumin and high β-globulin values may persist. Schneider, Lewis, and McCullagh (1946) have shown that plasma-protein values approaching normal may be obtained in some patients with diabetic retinitis by giving high-protein diets. Nevertheless, when the vascular lesions are severe, the protein spectrum remains permanently abnormal. Rifkin and Petermann (1952) have determined the serum-protein pattern in the diabetic glomerulosclerosis syndrome which was first described by Kimmelstiel and Wilson (1936). In the cases described by Rifkin and Petermann (1952) the loss of much protein in the urine was reflected in the low concentration of serum-albumin. There was also a distinct increase in the α_2-globulins, and a slight increase in the β-globulins, but γ-globulin values were within the normal range. It is suggested that the electrophoretic pattern of the serum-proteins in the insulin-resistant patient (Table V) coincides with that of the glomerulosclerosis syndrome, but is distorted by high γ-globulin values which may have been superimposed by multiple infections.

Discussion

The subject of this investigation was a middle-aged, obese diabetic woman who suffered from degenerative vascular and renal lesions. The pathological changes were in general typical of those which occur in cases of prolonged and poorly controlled diabetes (Bell, 1953). As the result of a minor cutaneous infection she gradually developed insulin resistance, and lapsed into coma in spite of the administration of 500 units of insulin per day. Recovery from coma was followed by several episodes of infection accompanied by a spectacular rise in the insulin requirements. Although the diabetic state was ultimately controlled

at the level of 600 units of insulin per day, this requirement persisted until death from coronary complications.

The novel feature of this case was the presence of a large amount of insulin in the blood. Although the insulin was not assayed, the experiments indicated that the circulation might contain about 1,000 to 1,500 units, and the total extracellular fluid possibly 3,000 to 4,000 units, at the height of the resistant state. The insulin was either free or reversibly bound to plasma-protein. It was available to exercise its normal effects, because it exerted a characteristic hypoglycaemic action in the rat and stimulated the formation of glycogen in isolated rat muscle. When insulin was withheld from the patient, the hypoglycaemic activity of the serum diminished almost to the point at which it was undetectable in the rat preparation. Experiments with protein fractions of the serum showed that the insulin was associated with the β-lipoproteins. Bornstein (1954) has recently found that insulin is carried in normal human plasma by a component of the β-lipoprotein fraction. The high concentration of blood-insulin was clearly due to the presence of the active insulin administered, and to its persistence in the circulation for a relatively long period. This fact is illustrated by the experiments of Figs. 2 and 3: in the former the hypoglycaemic action of the serum was not reduced to the limit of detection until insulin therapy had been withheld for 57 hours, and in the latter the magnitude of the hypoglycaemic action was directly related to the level of insulin dosage.

Few conclusions can be drawn concerning the defect responsible for the insulin-resistant state. The possibility of faulty absorption is eliminated, since the blood contained a great excess of insulin and the patient was resistant to insulin given subcutaneously or intravenously. It is improbable that antibodies to insulin were responsible. No insulin-inhibiting factor, such as that described by Bornstein (1953) and Bornstein and Park (1953), was detected in the blood. Changes in the plasma-protein spectrum ran parallel with the declining phase of insulin requirement, but there is no evidence to connect these events in causal relationship. The accumulation of insulin in the blood appears to exclude the possibility of abnormally fast destruction in the liver or elsewhere (Mirsky and Broh-Kahn, 1949; Bruch, 1950). It seems likely that the defect was in the tissues at the site of action of insulin. The present investigation does not provide evidence which would help to distinguish hormonal factors from other factors that might operate at this site to produce insulin resistance. The striking correlation in time between the episodes of staphylococcal infection and the increase of insulin requirement suggests a causal relationship which might conceivably be located at the site of insulin action.

The authors are much indebted to Dr. F. B. Cousins for carrying out the electrophoretic analysis of serum, and to Dr. R. A. Rodda and Dr. J. Brueckner, of the Department of Pathology, the former for the post-mortem report and the latter for plasma-protein estimations.

Summary

1. An unusual case of extreme and prolonged insulin resistance is described. The patient was an obese diabetic woman of middle age, who died of vascular complications. Insulin resistance developed during an episode of infection, attained spectacular levels, and persisted until death a year later.

2. The remarkable feature of the case was the presence of a large amount of insulin associated with the β-lipoprotein of the blood-plasma. The patient's serum induced hypoglycaemia in the rat, and stimulated glycogen formation in isolated rat muscle. The evidence shows that insulin resistance was not due to inadequate absorption or to excessive inactivation of insulin, but to defective response in the tissues. The plasma-protein spectrum changed as the insulin requirement diminished.

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